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SYNTHESIS OF IMPROVED ANTILEISHMANIAL AND ANTITRYPANOSOMAL DRUGS TREATMENT AND PROPHYLAXIS

ANNUAL REPORT

By

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Modified 8-Diethylaminohexylamino-6-methoxy-4-methylquinoline
Amidoximes

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

The program is directed at the preparation of improved antileishmanial and antitrypanosomal drugs. During the past year 13 target compounds were submitted for testing against L. donovani, T. rhodesiense and T. cruzi. Two candidate antileishmanials are modified 8-aminoquinolines. Eleven compounds were directed primarily against T. cruzi. These included seven 2,2-di(or tri)aryldimethyl(or dihydro)aminomethylethylenes and four 1-amidoximino-2,2-di(or tri)diarylethylenes.

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FOREWORD

The work described herein was performed under Contract No. DAMD17-84-C-4210 for the Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Walter Reed Army Medical Center. This Annual Progress Report covers the 12 month period ending 31 August 1986.

Citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organizations.

ACKNOWLEDGMENT

The work was performed under the general direction of Dr. C.L. Stevens, Principal Investigator. Dr. A. Markovac served as Associate Investigator and Dr. D.J. Dagli, Dr. G.S. (Ken) Wu and Mr. R.L. Kalamas as Senior Research Chemists with A.B. Ash as Program Manager.

The timely advice and assistance of Dr. Robert R. Engle, the COTR, is gratefully acknowledged.

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SYNTHESIS OF IMPROVED ANTILEISHMANIAL AND ANTITRYPANOSOMAL DRUGS

TREATMENT AND PROPHYLAXIS

1. INTRODUCTION AND BACKGROUND

Work under the current contract was initiated September 1, 1984. This new program, representing a continuation and extension of work performed under a prior contract (1), is intended to provide synthesis support for the research effort against leishmaniasis and trypanosomiasis by the U.S. Army Medical Research and Development Command. The accomplishments under the prior contract, including all of the available biological data together with references to the Annual Reports for preparation details, have been presented and discussed in the Final Summary Report (1). A total of 56 target candidate drugs were submitted in several general structural categories as follows: analogs of active leishmaniacide WR 6,026, 8-[(6-diethylaminohexyl)amino]-6-methoxy-4-methylquinoline (15), 7-aminoquinolines (3), 3-aminoquinolines (2) 4-amino-2,6-substituted-pyridines (1), aryl/heterocyclic bis(amidoximes) and bis(amidines) (20), bis(amidoxime) analogs (4) of four clinical bis(amidines) (4) and HOE 668 and structural modifications (7).

Among the 56 compounds, promising new leads against L. donovani were obtained in the 8-aminoquinoline series by some 15 modifications of the basic WR 6,026 structure, largely by incorporating additional methoxy groups in the 2- and/or 5- position, as well as various side chain modifications of WR 6,026. Significant reductions in toxicity were achieved in a number of instances while retaining a high degree of activity. Some modest success against L. donovani was observed also with two bis(amidoximes) in the styryl/heterocyclic category which are comparable in activity to the commercial drugs stilbamidine and pentamidine, combined with significantly reduced toxicity.

Another successful result under the past program was the acquisition of new candidate trypanocides with a high degree of activity against T. rhodesiense. The drugs are effective administered both PO as well as SC and possess excellent toxicity characteristics. For example, 2,6-bis(4-amidoximinophenyl)-4-methylpyridine, WR 248,936, is active at 0.83 mg/kg, both PO and SC, with a minimum toxic dose of 424 mg/kg or higher, respectively. On the other hand, no compounds active against the refractory T. cruzi, indigenous to South and Central America, were found and more emphasis under the current contract was placed on this area.

Current Contract (9/1/84 through 8/30/86)

The structures of the 22 compounds submitted in the past two years are shown in Figure 1.

First Year

The work performed under the current contract from September 1, 1984 through August 31, 1985 was reported and discussed in the first Annual Progress Report (2). The work followed very closely the compounds recommended in our Proposal dated March 7, 1984 in response to RFP-DAMD17-84-R-0041. The compounds therein were assigned PC (proposed compound) numbers and all of the nine compounds, SNL-109 through SNL-117 representing first year work were taken from the Proposal.

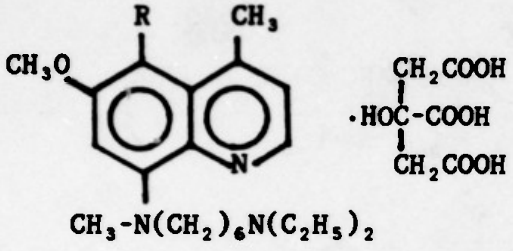
Second Year

In the past year ending August 31, 1986, 13 new compounds were prepared and submitted, three in the six months ending February 28, 1986. Two of these, SNL-118 and 119, were modifications of the 8-aminoquinoline WR 6026. The third, SNL-120, represented the first modification of the Wellcome 2,2-diaryl-dialkylaminomethyl ethylenes, which are reported to be effective orally against Peruvian strains of T. cruzi in mice (3a,b,c).

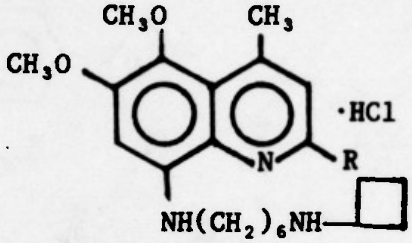
The other 10 compounds of the second year were prepared in the six months ending August 31, 1986. Nine of the ten compounds were modifications of the Wellcome trypanocide 353C, the most promising reported by the Wellcome Research Laboratories (3). This work also follows closely that outlined in our Proposal.

FIGURE NO. 1

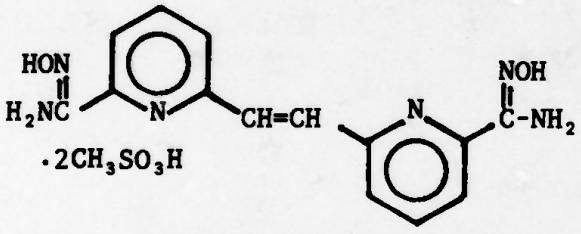
COMPOUNDS PREPARED TO DATE UNDER THE CURRENT CONTRACT
(1 September 1984 - 31 August 1986)
Year No. 1



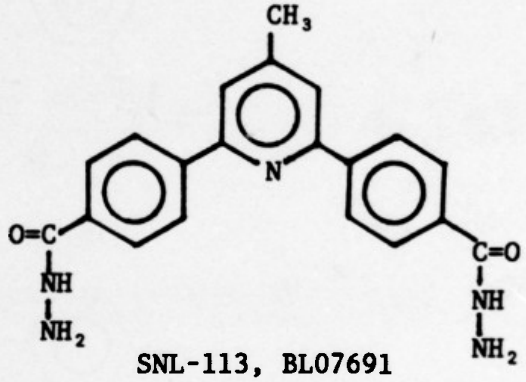
SNL-109, R = H, BK99121
SNL-111, R = OCH_3, BL03808



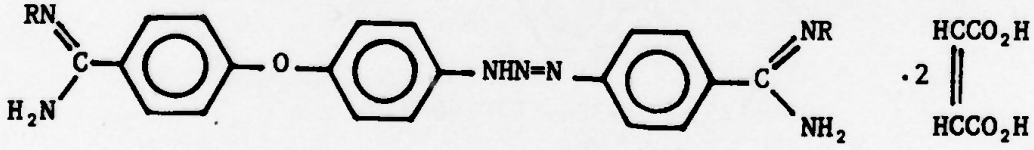
SNL-112, R = H, BL05571
SNL-114, R = OCH_3, BL07682



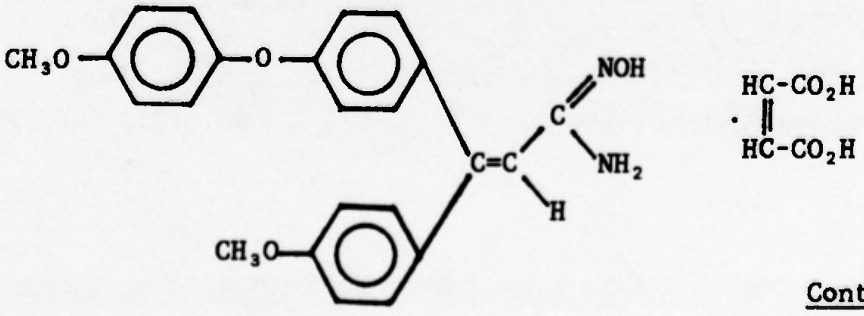
SNL-110, BL00432



SNL-113, BL07691



SNL-115, R = OH, BL08401
SNL-116, R = H, BL09533

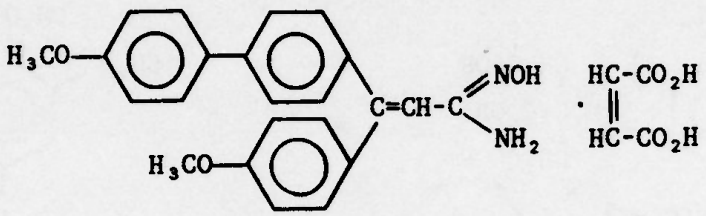


Continued

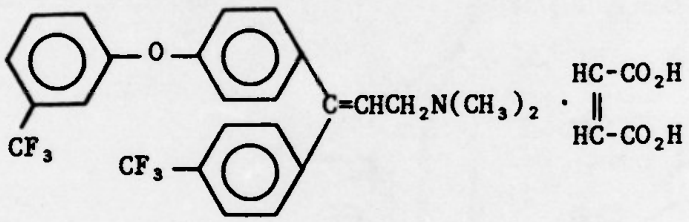
SNL-117, BL09524

FIGURE 1, Continued

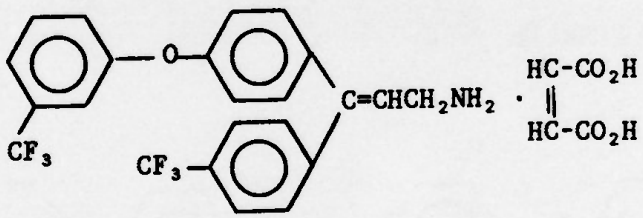
Year No. 2
Second Six Months



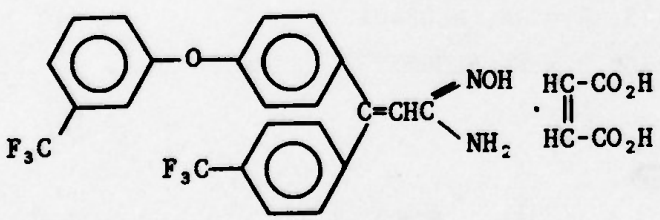
SNL-121, BK40799, AM-04-28



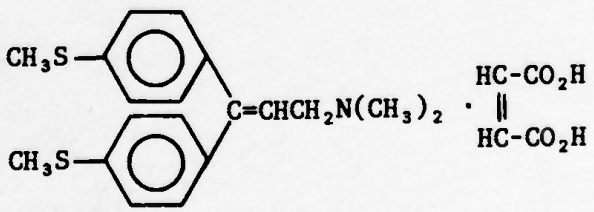
SNL-122, BL19333, DJD-06-268



SNL-123, BL19324, DJD-06-270



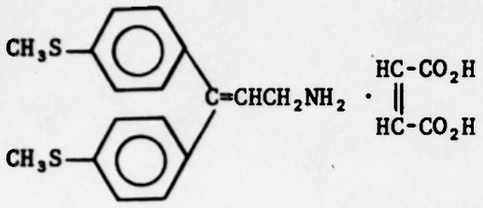
SNL-124, BL19315, RK-04-154



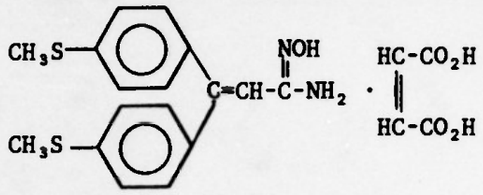
SNL-125, BL20336, DJD-06-288

Continued

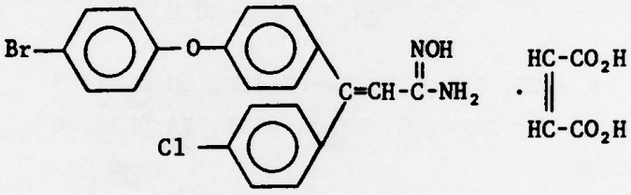
FIGURE 1, Continued



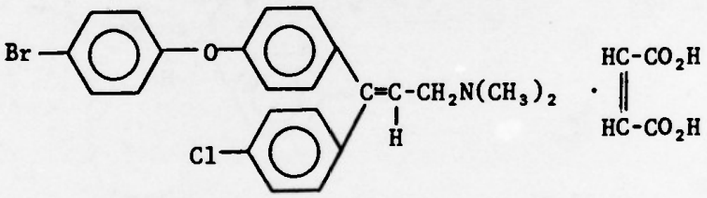
SNL-126, BL20345, DJD-06-293



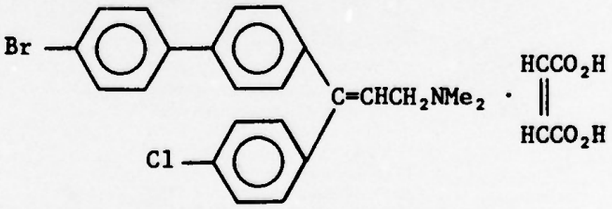
SNL-127, BL20354, DJD-06-295



SNL-128, BL21780, DJD-07-27



SNL-129, BL22205, DJD-07-32



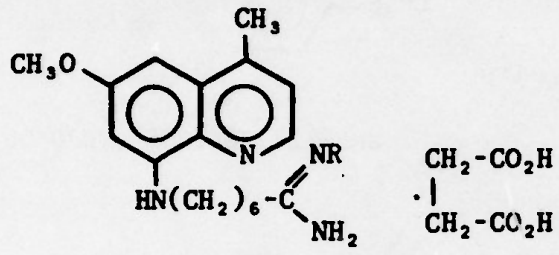
SNL-130, BL24003, DJD-07-44

Wellcome Research Laboratories 353C

(As Tartrate salt)

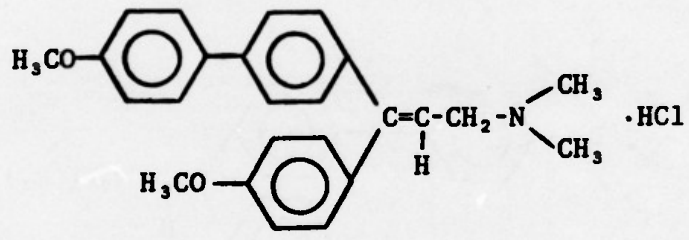
FIGURE 1, Continued

Year No. 2
First Six Months



R = OH, SNL-118, KW-08-188, BN BL12503

R = H, SNL-119, KW-08-211B, BN BL12790



SNL-120, DJD-06-210, BN BL18247

2. DISCUSSION OF WORK COMPLETED. BIOLOGICAL RATIONAL AND DATA.

The 22 compounds submitted in the past two years of the current contract are shown in Figure 1, pages 6-9. These compounds will be discussed briefly, both in terms of the biological rationale leading to their preparation, as well as the activity data available at this writing. Biological data for the 56 target compounds submitted under the prior contract were summarized in the Final Summary Report (1) and the 12 compounds submitted in the first year were discussed in the first Annual Progress Report (2). Some of the data for 56 prior-contract compounds will be tabulated herein for comparative purposes. In the past (second) year, 13 target compounds were submitted. These include three new candidate leishmaniacides (L. donovani), together with 10 trypanosomiacides directed against Chagas disease (T. cruzi). When the work-in-progress is completed, attention will be directed more actively to new leishmaniacides as suggested by the COTR. The 13 structures are shown in Fig. 1 as part of the Year No. 2 submissions.

2.1 Leishmaniacides

The major effort to date has been directed at modified 8-aminoquinolines. Thus, under the current contract in the past two years, six new examples were prepared: SNL-109, 111, 112, 114, 118 and 119 (see Figure 1). The rationale for their preparation is the high activity of WR 6026 against L. donovani (Hanson) represented by a Glucantime index of 474 (IM) and 708 (PO). The available biological data are shown in Table 1.

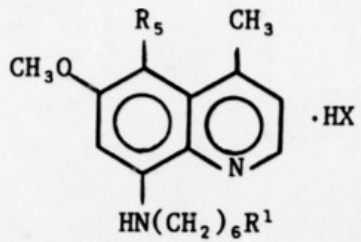
8-N^1-CH_3 Blocking Group: - The pair of 8-N^1-CH_3 blocked compounds, SNL-109 and 111, represent the use of a blocking N-methyl group to prevent the metabolic conversion of the drug to a 5,8- or a 7,8-iminoquinone in order to assess the impact upon the activity and/or toxicity relative to the parent compounds. Referring to Table 1, no data are yet available for SNL-109 which is WR 6026 containing a 8-N^1 blocking methyl group. However, SNL-111, which bears the toxicity-inducing (usually) 5-methoxy group (see earlier data for WR 226,292), shows a minimum toxic dose of 832 mg/kg and a 100% suppression of parasites at 52 mg/kg (lowest dose tested). While the data are limited, the results are nevertheless promising.

8-N^6-Cyclobutyl Side Chain Group: - Similarly, in the case of analogs bearing a cyclobutyl side-chain group (Table 1), the original compound, SNL-07, showed both promising activity and reduced toxicity relative to WR 6026. Accordingly, in the case of SNL-112, the activating but toxicity-inducting 5-methoxy group was again added; no data are yet available. However, some data are available for SNL-114, the 2-methoxy derivative, which shows 100% suppression of parasites at a dosage of 52 mg/kg, coupled with a sharply reduced toxicity (high minimum toxic dose of 832 mg/kg). Data at dose levels below 52 mg/kg are required to explore this promising lead further.

TABLE 1

ANTILEISHMANIAL ACTIVITY OF ANALOGS OF WR 6026 (IN PART)

L. donovani, hamster (Hanson) (IM)



SNL No.	WR No., Bottle No.	R^1	R_5	Other Groups	Min. Curative Doses, % Suppression mg/kg/day (x4)		Min. Toxic Dose	Glucantime Index, G
	6,026	$-NEt_2$	H	—	99.6/0.20	84/0.05	52	474
	226,292	$-NEt_2$	$-OCH_3$	—	100/0.20	68/0.05	>13 <52	401
17	242,896	$-NEt_2$	H	$2-OCH_3$	99.5/13	56/0.81	208(6/6T)	33
108	252,123	$-NEt_2$	$-OCH_3$	$2-OCH_3$	100/52(a)		208(6/6T)	7(a)
				$8-N^1$-Blocked Analogs				
109	253,904	$-NEt_2$	H	$8-N^1-CH_3$				
111	254,233	$-NEt_2$	$-OCH_3$	$8-N^1-CH_3$	100/52(a)		832(6/6T)	1(a)
				Cyclobutyl Sidechain Analogs				
07	239,374	$-NH-C_4H_7$	H	—	99.2/0.81	74/0.20	208(6/6T)	188,174
112	254,391	$-NH-C_4H_7$	$-OCH_3$	—				
114	BL07682	$-NH-C_4H_7$	H	$2-OCH_3$	100/52(a)		832(6/6T)	1(a)
				Amidoximino/Amidino Sidechain Groups				
118	BL12503	$-C(NH_2)=NOH$	H	—				
119	BL12790	$-C(NH_2)=NH_2$	H	—				

(a) Lowest Dose Tested.

8-N^6-Amidoximino/Amidino Sidechain Groups: - The most recent modifications of WR 6026 are SNL-118 and 119 in which the exterior 8-amino group is replaced by an amidoximino and amidino group, respectively. No data are yet available (Table 1) and the results are hard to predict.

Other: - Another candidate leishmaniacide of a different structural category is represented by 2,6-bis(4-hydrazidophenyl)-4-methylpyridine, SNL-113 (Fig. 1). This was prepared based on a suggestion by Peters and associates (4) who noted that the antituberculosis drug isoniazid had a remissive effect (tissue culture and animals) against L. mexicana, and a salutary clinical result in limited cases. While the clinical result was discounted later, the hydrazido group may be worth exploring as new leads are relatively scarce. Further, we note that HOE 668, a reportedly potent experimental leishmaniacide (5), contains a phenylhydrazone grouping.

2.2 Trypanosomiacides

The early effort (1) was directed at exploring the effect of a wide variety of bis(amidines) and bis(amidoximes) against T. rhodesiense (Rane/Ager) and T. cruzi (Ager, 1978, or Hanson, 1985).

Bis(amidoximes) and bis(amidines): - As reported in detail in the earlier work under the prior contract (1), considerable success against L. rhodesiense was achieved with a number of the title compounds as shown in Table 2 (for structures, see Figure A-1, Appendix A). Thus a number of compounds were active (SC) over a range of 0.11 to 0.83 mg/kg and SNL-28 (WR 248,396), 2,6-bis-(4-amidinophenyl)-4-methylpyridine dihydrochloride, was curative (PO) at 1.66 mg/kg.

In the current program, the preparation of 1,2-ethylene-bis-(6-amidoximino-2-pyridyl), SNL-110 (Fig. 1), was based on the high activity against T. rhodesiense exhibited by the closely related 2-amidoximino-6-(4-amidoximinostyryl)pyridine (SNL-36), WR 249,238, which gave a minimum curative dose of 6.55 mg/kg (x 1), both SC and PO (1). SNL-110 (WR 254,019) was curative (4/5C) at 13 mg/kg but it was inactive at 13 mg/kg (no oral data). Also the new submissions, SNL-115 and 116 are triazene structures relating to the commercial drug diminazene(berenil) with a phenoxy grouping; no data are available on these as yet.

Some 16 of the title bis(amidoximes) and bis(amidines) were tested against T. cruzi (Ager); none were active, although two compounds bearing a phenyl sulfide group showed minimal curative activity (SNL-96 and SNL-101 (1)). The results, in part, led to the work discussed below directed specifically against T. cruzi (3).

TABLE 2

ANTITRYPANOSOMAL DATA. SELECTED BIS(AMIDOXIMES) AND BIS(AMIDINES)

AO = Bis(amidoxime), AM = Bis(amidine)

SNL No.	WR or BN No.	Type Cpd.	T. rhodesiense Rane/Ager, five mice (SC) Min. Curative Dose	100% Curative Dose(5/5C)	Min. Toxic Dose	Rane,[a] five mice, Min. Toxic Dose
For Structures, see Figure 2.			mg/kg(x1)			
			A. Bis(aryl) Heterocycles			
28	248,396	AO	0.83(5C)	0.83	>424	
29	248,535	AM	0.11(1C)	0.42	424	160(1T)
47	249,698	AM	0.21(2C)	0.83	424	640(5T)
54	250,262	AM	0.21(2C)	0.83	106	160(4T)
107	252,070	AM	0.11(1C)	0.42	106,212	NA
			B. HOE 668, SNL-77 and Thio Analog SNL-96			
77	245,720	AM	0.11(2C)	0.83	424	>640(0T)
96	251,336	AM	0.83(4C,5C)	0.83	212	
			C. Commercial Drugs and Bis(amidoxime) Analogs			
			Pentamidine Dimethanesulfonates			
63	250,385	AO	0.83 (1C)	1.66	106	640(4T)
64	4,931	AM	0.83 (2C)	1.66	106	640(5T)
			Diminazene (Berenil) Dimaleates			
67	250,483	AO	0.11 (1C)	0.83	212	
68	27,800	AM	0.01 (1C)	0.11	106	160(3T)

a) *P. berghei* antimalarial test.

1,1-Diaryl-2-(dimethylaminomethyl)ethylenes and 1,1-Diaryl-2-(amidoximino)ethylenes

A recent paper by workers at the Wellcome Research Laboratories described a powerful trypanocide effective orally in mice against Peruvian strains of T. cruzi (3a). The compound designated 353C, has been resynthesized and submitted recently (8/28/86) to WRAIR for comparitive purposes (SNL-130, Figure 1).

Accordingly, as shown in Figure 2 (Part A) a series of five 2-dialkylaminomethylethylenes and one 2-aminomethyl analog were prepared representing new structures to our best knowledge.

In addition, five of the intermediates 1,1-diaryl-2-cyano-ethylene intermediates were converted to the corresponding 2-amidoximinoethylenes.

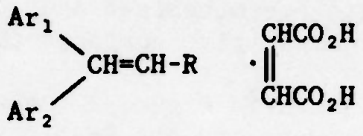
All of the structures are maleic acid salts except SNL-120 which is a hydrochloride salt. No T. cruzi data are available at this writing.

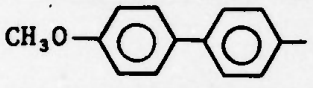
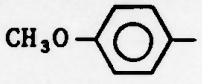
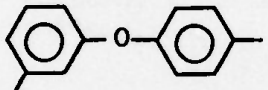
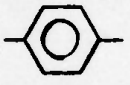
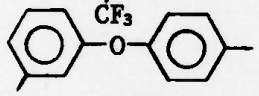
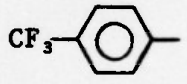
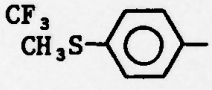
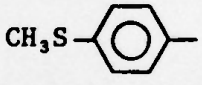
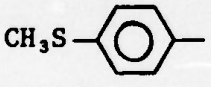
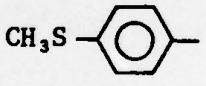
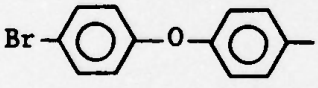
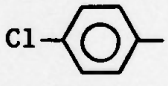
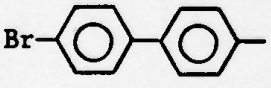
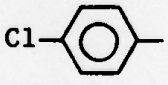
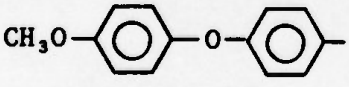
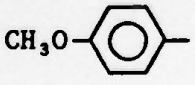
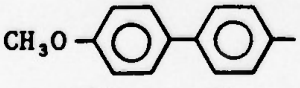
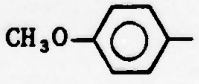
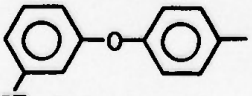
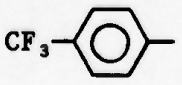
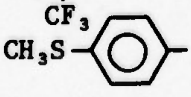
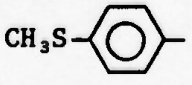
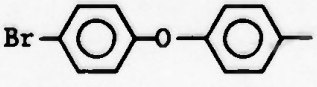
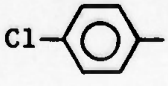
FIGURE 2

1,1-DIARYL-2-(DIMETHYLAMINOMETHYL)ETHYLENES

1,1-DIARYL-2-(AMIDOXIMINO)ETHYLENES

(See Also Fig. 1)



Bottle No. (SNL No.)	Ar_1	Ar_2	R
A. 1,1-Diaryl-2-(dimethylaminomethyl)ethylenes			
BL18247(a) (120)			$-CH_2N(CH_3)_2$
BL19333 (122)			$-CH_2N(CH_3)_2$
BL19324 (123)			$-CH_2NH_2$
BL20336 (125)			$-CH_2N(CH_3)_2$
BL20345 (126)			$-CH_2NH_2$
BL22205 (129)			$-CH_2N(CH_3)_2$
BL24003 (130)			$-CH_2N(CH_3)_2$
B. 1,1-Diaryl-2-(Amidoximino)ethylenes			
BL09524 (117)			$-C(NH_2)=NOH$
BK40799 (121)			$-C(NH_2)=NOH$
BL19315) (124)			$-C(NH_2)=NOH$
BL203541 (127)			$-C(NH_2)=NOH$
BL21780 (128)			$-C(NH_2)=NOH$

(a) HCl Salt

3. SYNTHESIS RESULTS AND DISCUSSION

The 13 target compounds prepared in the past year are discussed below.

3.1 8-[(6-Amidoximinohexyl)amino]-6-methoxy-4-methylquinoline Succinate (SNL-118, BL12503)

3.2 8-[(6-Amidinohexyl)amino]-6-methoxy-4-methylquinoline Succinate (SNL-119, BL12790)

The two target compounds were prepared by the three-step sequence shown in Chart No. 1.

8-Amino-6-methoxy-4-methylquinoline, available in-house from Walter Reed antimalarial preparative work, was treated with 7-bromoheptanonitrile in the presence of diisopropyl ethylamine to give the intermediate 8-(6-cyanohexyl)aminoquinoline 1 (75%). The nitrile 1 was converted to the amidoxime 2 (64%), isolated as the succinate salt. A 5.0 g sample was shipped to Walter Reed on December 2, 1985 as Code No. KW-08-188, BN BL12503.

The amidoxime 2 was reduced with hydrogen and Raney nickel catalyst to afford the amidine 3 (65%), also isolated as the succinate salt. A 6.0 g sample was shipped to Walter Reed on January 8, 1986 as Code No. KW-08-211B, BN BL12790.

3.3 1-(4-Methoxyphenyl)-1-(4'-methoxy-4-biphenylyl)-3-dimethylaminoprop-1-ene hydrochloride (SNL-120, BL18247)

The five-step sequence to the title compound is shown in Chart No. 2. While the Wellcome Laboratory workers prepared some 130 analogs (3), this 4'-methoxybiphenyl-4-methoxyphenyl analog SNL-120 was selected, in part, because it was not reported by them.

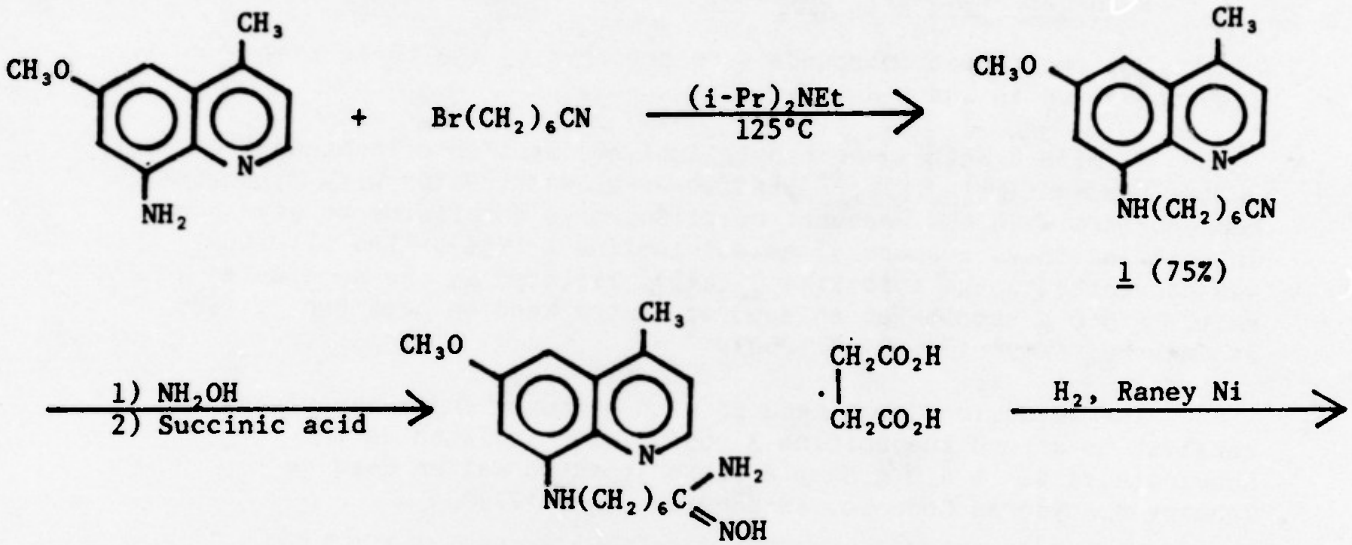
In general, the sequence followed the procedures used by Wellcome workers (3). The first step is a fairly conventional Friedel Craft reaction except that the alkylation of 4-methoxybiphenyl with 4-methoxybenzoyl chloride gave various by-products. This complicated the workup and led to a low yield of the intermediate diaryl ketone 1 (17-19%). [Even in the case where benzene was acylated with 4-methoxybiphenoyl chloride the yields were low (6), although Johnson et al. (7) in a related reaction reported a 62% yield of pure product in the treatment of 4-methoxybiphenyl with acetyl chloride to form 4-(4-methoxyphenyl)acetophenone].

Treatment of intermediate 1 with acetonitrile in the presence of sodamide gave an acceptable yield of the 3-hydroxypropionitrile 2 (82%) as described earlier for a diphenyl ether analog ((2) p. 44).

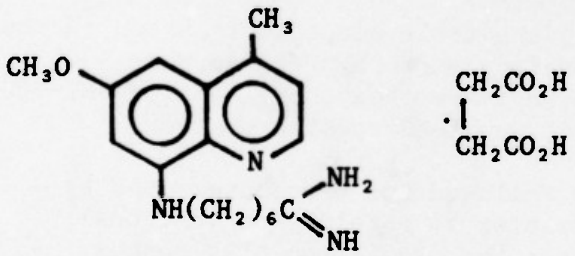
CHART NO. 1

8-[(6-AMIDOXIMINOHEXYL)AMINO]-6-METHOXY-4-METHYLQUINOLINE SUCCINATE (SNL-118; BN BL12503)

8-[(6-AMIDINOHEXYL)AMINO]-6-METHOXY-4-METHYLQUINOLINE SUCCINATE (SNL-119; BN BL12790)



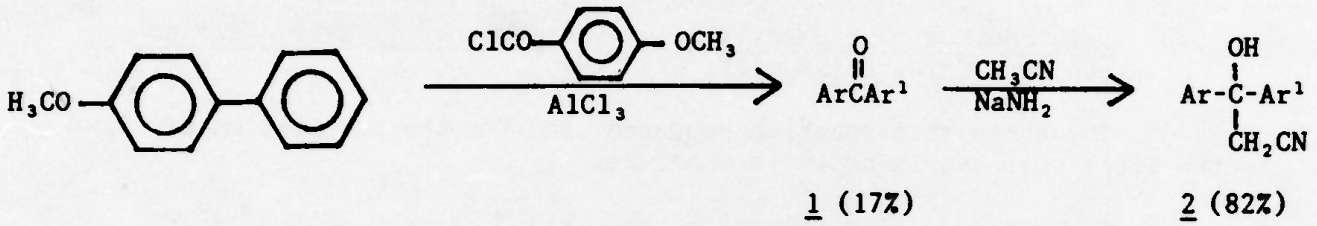
2, SNL-118 (64%); BN BL12503
KW-08-188



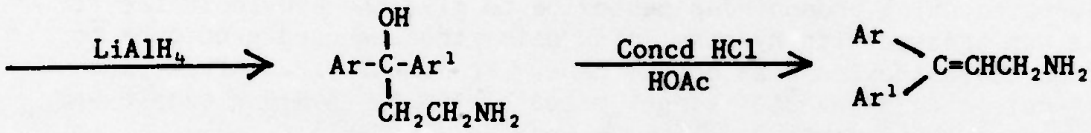
3, SNL-119 (65%); BN BL12790
KW-08-211B

CHART NO. 2

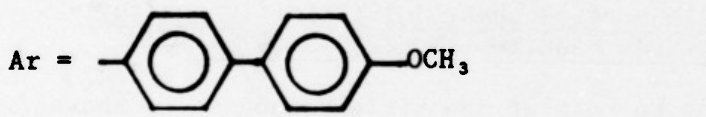
1-(4-METHOXYPHENYL)-1-(4'-METHOXY-4-BIPHENYLYL)-
3-DIMETHYLAMINOPROP-1-ENE HYDROCHLORIDE (SNL-120, BN BL18247)

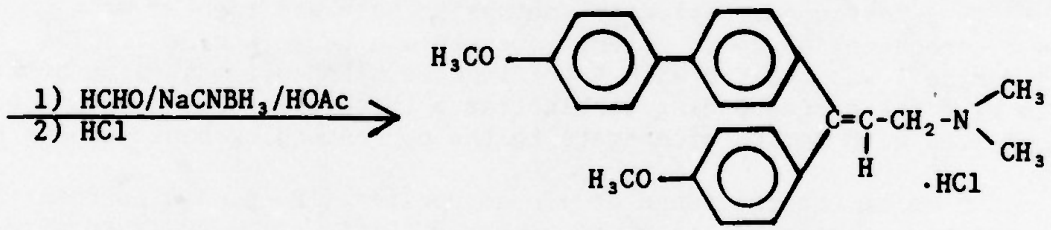


1 (17%) 2 (82%)



3 (84%) 4 (80%)





5 (23%), SNL-120,
BL18247, DJD-06-210

Reduction of intermediate 2 with lithium aluminum hydride gave the 3-hydroxypropyl amine 3 (84%) which was dehydrated readily with mixed acids to the allylic amine 4 (80%). Dimethylation of the allylic amine by the Eschweiler-Clark method failed. The newer formaldehyde-cyanoborohydride procedure of Borch and Hassid (8) gave a crude product which required extensive purification to give the target diaryl dimethylaminomethyl ethylene 5 (23%). A 4.5 g sample was shipped January 23, 1986 as Code No. DJD-06-210, BL18247.

3.4 1-(4'-Methoxy-4-biphenylyl)-1-(4-methoxyphenyl)-2-amidoximino-ethylene Maleate (SNL-121, BK40799)

The three-step reaction sequence used for the preparation of the title compound is shown in Chart No. 3.

3-Hydroxy-3-(4'-methoxy-4-biphenylyl)-3-(4-methoxyphenyl)-propionitrile, available from the synthesis of SNL-120, was dehydrated using phosphorous pentoxide to give the acrylonitrile 1. This was treated with hydroxylamine using the standard procedure to afford the amidoxime 2 as a free base. Treatment of the free base with maleic acid gave the target maleate salt 2. A 5.0 g sample was shipped to WRAIR March 31, 1986 as Code No. AM-04-28.

3.5 1-(3'-Trifluoromethylphenoxy-4-phenyl)-1-(4-trifluoromethyl-phenyl)-3-dimethylaminoprop-1-ene Maleate (SNL-122, BL19333)

3.6 1-(3'-Trifluoromethylphenoxy-4-phenyl)-1-(4-trifluoromethyl-phenyl)-3-aminoprop-1-ene Maleate (SNL-123, BL19324)

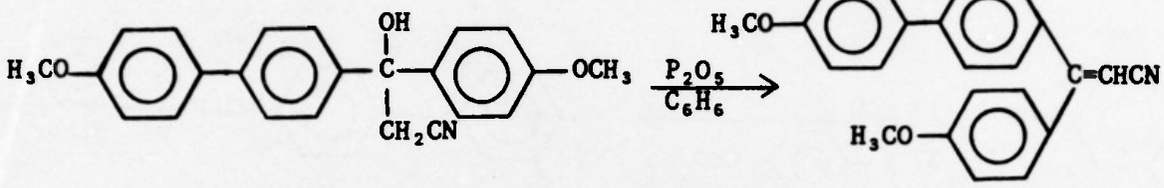
The six-step sequence to both of the title compounds is shown in Chart No. 4.

3-Trifluoromethylphenol potassium salt was treated with 4-fluorobenzaldehyde to afford intermediate benzaldehyde 1. The aldehyde 1 was treated with 4-trifluoromethylphenyl magnesium bromide to give the corresponding carbinol as a thick oil. The carbinol was oxidized with sodium dichromate to the corresponding benzophenone 2.

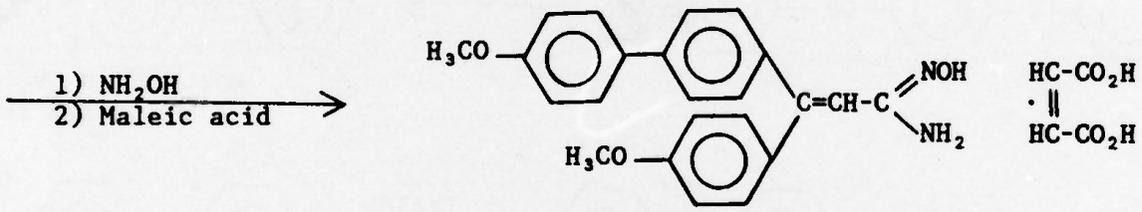
Using the procedure developed earlier ((2) p. 44) in this laboratory, intermediate 2 was condensed with acetonitrile to give the hydroxypropionitrile 3. The latter was reduced with lithium aluminum hydride to give the 3-hydroxypropylamine 4 which was dehydrated with mixed acids to the allylic amine 5. A portion of this was converted to the maleate salt 5a, SNL-123 and submitted as Code No. DJD-06-270, BL19324, 5.0 g. The balance of the allylic amine 5 was dimethylated using the formaldehyde-cyanoborohydride procedure ((1) p. 24) to give the target dimethylamine 6 as a free base. This was treated with maleic acid to yield the target maleate 6, SNL-122, submitted as Code No. DJD-06-270, BL19333, 7.5 g. Both of the targets were submitted April 14, 1986.

CHART NO. 3

1-(4'-METHOXY-4-BIPHENYLYL)-1-(4-METHOXYPHENYL)-2-AMIDOXIMINOETHYLENE MALEATE (SNL-121, BK40799)



(Compound 2, Chart No. 2) 1 (80%)



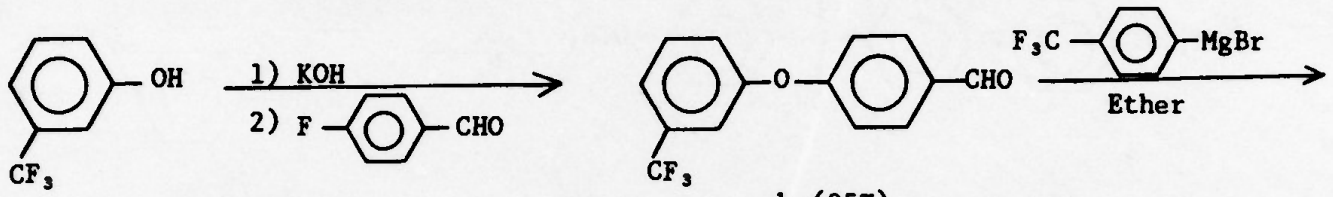
2, SNL-121, BK40799,
AM-04-28

Yields: Free base: 37% from 1
Maleate salt 2: 69% from 2, free base

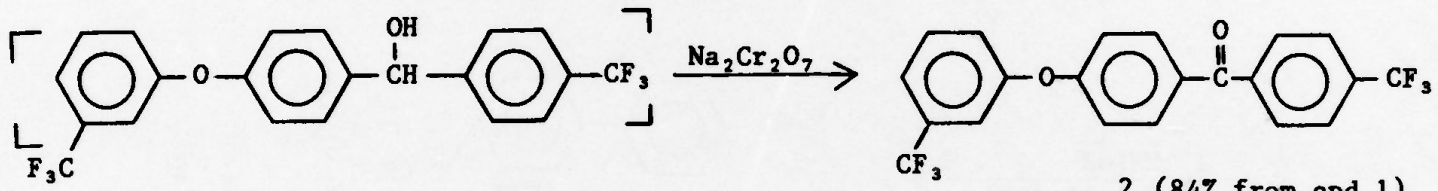
CHART NO. 4

1-(3'-TRIFLUOROMETHYLPHENOXY-4-PHENYL)-1-(4-TRIFLUOROMETHYLPHENYL)-3-DIMETHYLAMINOPROP-1-ENE MALEATE (6, SNL-122, BL19333)

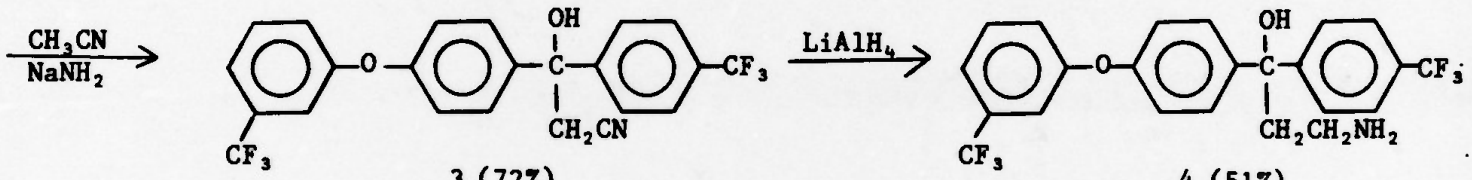
1-(3'-TRIFLUOROMETHYLPHENOXY-4-PHENYL)-1-(4-TRIFLUOROMETHYLPHENYL)-3-AMINOPROP-1-ENE MALEATE (5a, SNL-123, BL19324)



1 (85%)

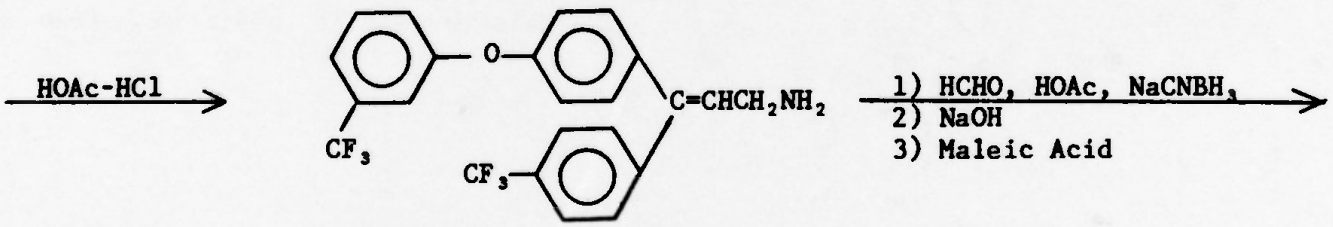


2 (84% from cpd 1)

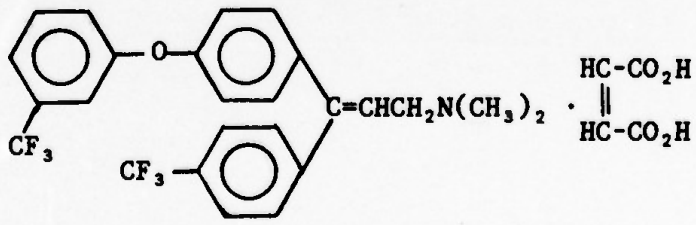


3 (72%)

4 (51%)



5 Free Base, 79% from 4
5a Maleate Salt, SNL-123
BL19324, DJD-06-270, Yield: 93% from 5 free base.



6 SNL-122, BL19333, DJD-06-268
Yields: 44% from 5, free base; 88% from 6 free base.

3.7 1-(3'-Trifluoromethylphenoxy-4-phenyl)-1-(4-trifluoromethyl-phenyl)-2-amidoximinoethylene Maleate (SNL-124, BL19315)

The target compound SNL-124 was prepared using the sequence shown in Chart No. 5.

Hydroxypropionitrile (compound 3, Chart No. 4), prepared according to the procedures described above in sections 3.5 and 3.6, was dehydrated using phosphorus pentoxide to give the acrylonitrile 1. Treatment of 1 with hydroxylamine afforded the amidoxime free base which was converted to the target maleate salt 2, SNL-124, BL19315. A 5.0 g sample was submitted April 14, 1986 as Code No. RK-04-154

3.8 Bis(4-methylthiophenyl)-3-dimethylaminoprop-1-ene Maleate (6, SNL-125, BL20336)

3.9 1-Bis(4-Methylthiophenyl)-3-aminoprop-1-ene Maleate (5a, SNL-126, BL20345)

The six-step reaction sequence to the above target compounds is shown in Chart No. 6.

4-Methylthiobenzoic acid was reacted with phosphorous pentachloride to give the corresponding acid chloride 1. The latter was condensed with thioanisole (Friedel Crafts) to yield bis(4-methylthiophenyl)ketone 2. Condensation of 2 with acetonitrile gave the intermediate hydroxypropionitrile 3 which was reduced ($LiAlH_4$) to the hydroxypropyl amine 4. This intermediate was dehydrated with mixed acids to give the allylic amine 5. A portion of 5 was treated with maleic acid to yield the target maleate salt 5a, SNL-126, BL20345. A 4.0 g sample was submitted May 28, 1986 as Code No. DJD-06-293.

In the final step compound 5, free base, was dimethylated using the standard formaldehyde cyanoborohydride procedure to give the target dimethylamine 6, free base. Treatment of the free base with maleic acid gave the above target maleate salt 6, SNL-125, BL20336, 5 g submitted May 28, 1986 as Code No. DJD-06-288.

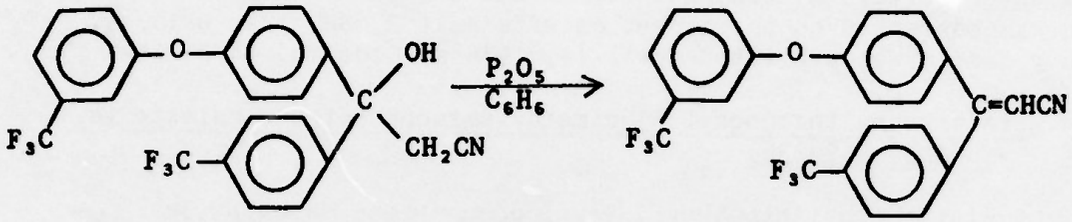
3.10 1-Bis(4-methylthiophenyl)-2-amidoximinoethylene Maleate (SNL-127, BL20354)

The two-step reaction sequence is shown in Chart No. 7.

The starting hydroxypropionitrile (compound 3, Chart No. 6) was dehydrated with mixed acids to give the acrylonitrile 1. Using the standard procedure, the nitrile 1 was treated with hydroxylamine to give the amidoxime free base which was converted to the target maleate salt 2, SNL-127, BL20354. A 4.0 g sample was submitted May 28, 1986 ad Code No. DJD-06-295.

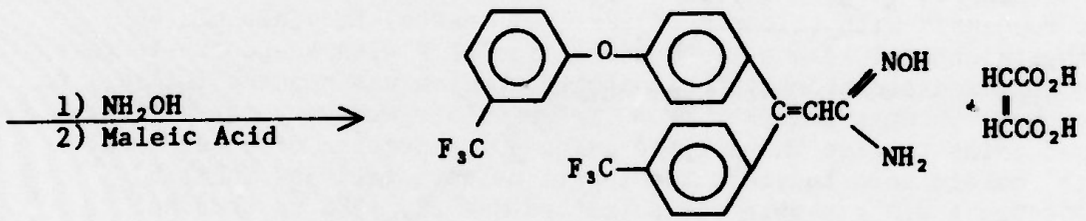
CHART NO. 5

1-(3'-TRIFLUOROMETHYLPHENOXY-4-PHENYL)-1-(4-TRIFLUOROMETHYLPHENYL)-2-AMIDOXIMINOETHYLENE MALEATE (SNL-124, BL19315)



Compound 3 from Chart No. 4

1 (syrup)

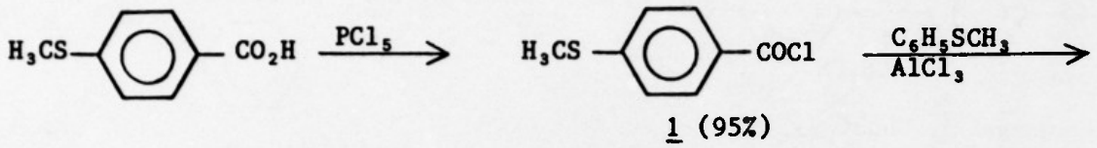


2, SNL-124, BL19315, RK-04-154
Yield: 44% from the starting propionitrile.

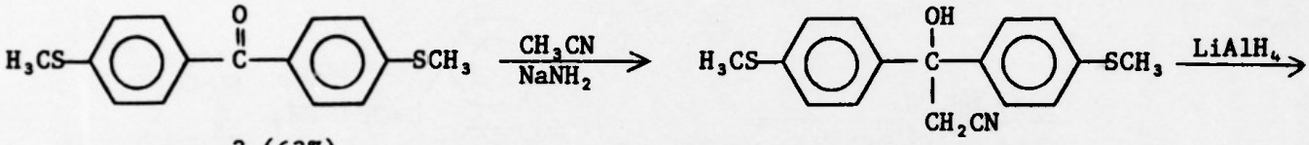
CHART NO. 6

1-BIS(4-METHYLTHIOPHENYL)-3-DIMETHYLAMINOPROP-1-ENE MALEATE (5, SNL-125, BL20336)

1-BIS(4-METHYLTHIOPHENYL)-3-AMINOPROP-1-ENE MALEATE (5a, SNL-126, BL20345)

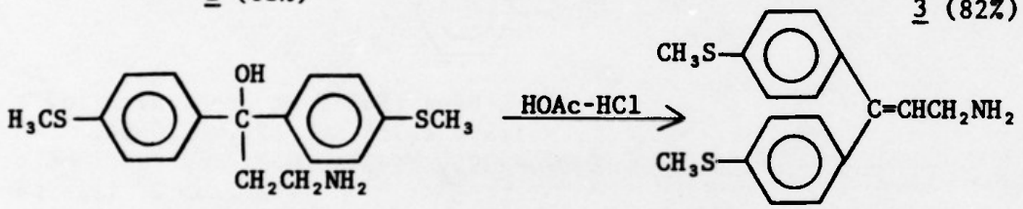


1 (95%)



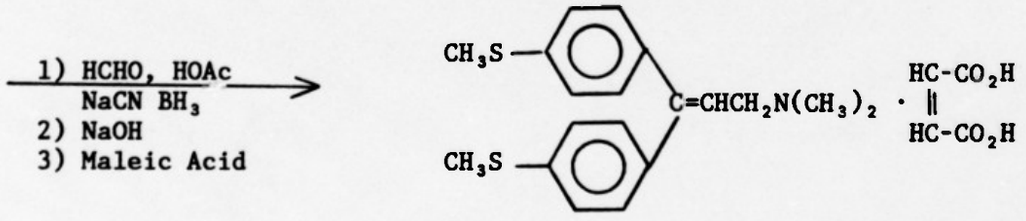
2 (63%)

3 (82%)



4 (88%)

5, Free Base 74% from 4
5a, Maleate Salt, SNL-126
BL20345, DJD-06-293
Yield: 100% from 5 free base

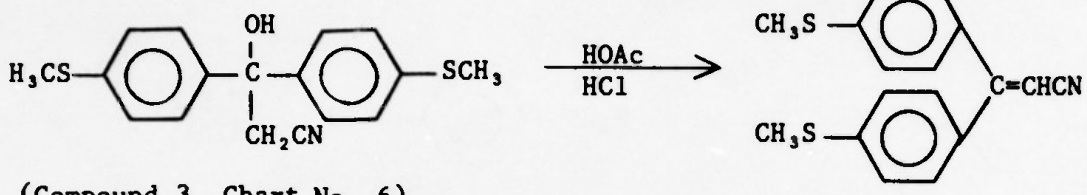


6, Free Base, 56% from 5 free base.
6 Maleate Salt, SNL-125, BL20336
DJD-06-288, Yield: 52% from 5 free base;
93% from 6 free base.

CHART NO. 7

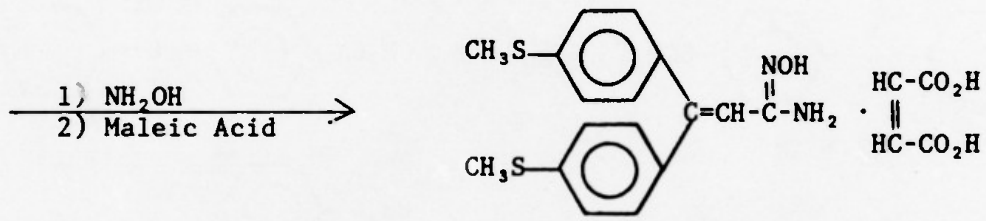
1-BIS(4-METHYLTHIOPHENYL)-2-AMIDOXIMINOETHYLENE

MALEATE (SNL-127, BL20354)



(Compound 3, Chart No. 6)

1 (oil)



2, Free Base (54% from propionitrile)
2, Maleate salt, SNL-127, BL20354,
DJD-06-295, Yields: 35% from pripionitrile;
64% from 2, free base.

3.11 1-(4'-Bromophenoxy-4-phenyl)-1-(4-chlorophenyl)-2-amidoximino-ethylene Maleate (SNL-128, BK21780)

The above target was prepared using the multistep synthesis shown in Chart No. 8. The first three steps are similar to those described above in Sections 3.5 and 3.6 and shown in Chart No. 4.

4'-Bromophenoxy-4-benzaldehyde (1) was prepared by condensing 4-bromophenol with 4-fluorobenzaldehyde. The aldehyde 1 was treated with 4-chlorophenylmagnesium bromide to give the corresponding carbinol (not shown) which was oxidized to give the benzophenone 2. Compound 2 was condensed with acetonitrile to give hydroxypropionitrile 3 which was dehydrated readily to afford the diarylacrylo nitrile 4. In the final step, the nitrile 4 was converted to the amidoxime free base which was treated with maleic acid to yield the target amidoxime maleate 5, SNL-128, BK21780. A 7.5 g sample was submitted July 26, 1986 as Code No. DJD-07-27.

3.12 1-(4'-Bromophenoxy-4-phenyl)-1-(4-chlorophenyl)-3-dimethyl-aminoprop-1-ene Maleate (SNL-129, BL22205)

The two-step reaction sequence is shown in Chart No. 9.

The starting material for the above target was the benzophenone (compound 2, Chart No. 8) which was condensed (Wittig reaction) with(2-dimethylaminoethyl)triphenylphosphonium bromide (Aldrich) to give the corresponding crude dimethylamine derivative 1, free base. This was treated with maleic acid to give the target maleate salt 2, SNL-129, BL22205. A 6.5 g sample was submitted August 7, 1986 as Code No. DJD-07-32.

3.13 1-(4'-Bromo-4-biphenylyl)-1-(4-chlorophenyl)-3-dimethylamino-prop-1-ene Maleate (2, SNL-130, BL24003)

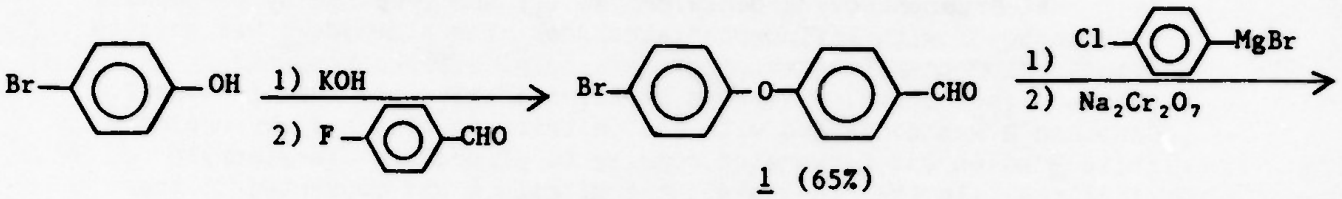
The target compound, SNL-130, is the maleate salt of compound 353C reported by the Wellcome Research Laboratories to be a powerful trypanocide effective orally against Peruvian strains of T. cruzi (3a).

The synthesis route shown in Chart No. 10 is essentially the same as that reported in the literature (3b). The benzophenone 1, obtained by the Friedel Crafts condensation of 4-bromobiphenyl and 4-chlorobenzoyl chloride, was condensed with commercially-available (2-dimethylaminoethyl)triphenylphosphonium bromide (Wittig reaction) to give the target compound 2 as a free base. After extensive purification to remove unreacted benzophenone 1 and other by-products, the free base was converted to the title maleate salt 2 (SNL-130, BL2003). A 4.5 g sample was submitted August 31, 1986 as Code No. DJD-07-44.

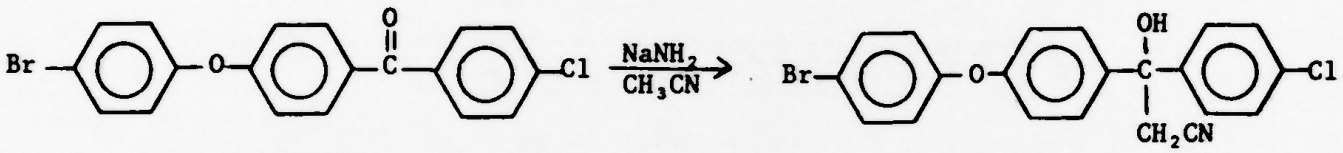
CHART NO. 8

1-(4'-BROMOPHENOXY-4-PHENYL)-1-(4-CHLOROPHENYL)-2-

AMIDOXIMINOETHYLENE MALEATE (SNL-128, BL21780)

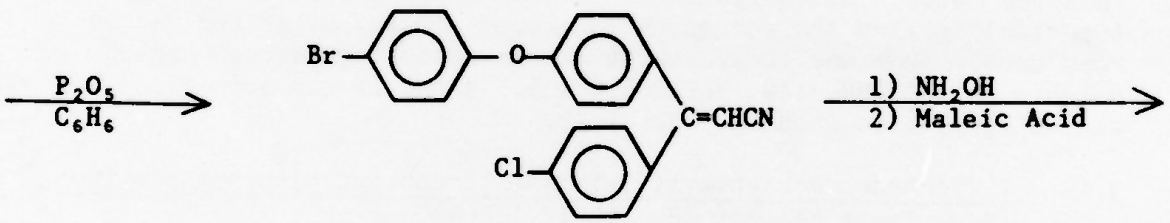


1 (65%)

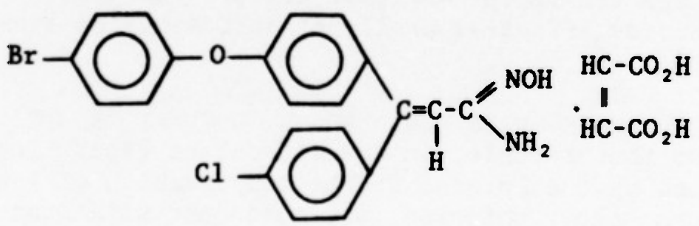


2 (49%)
Intermediate carbinol, 54%
Ketone 2, from carbinol, 91%

3 (61%)



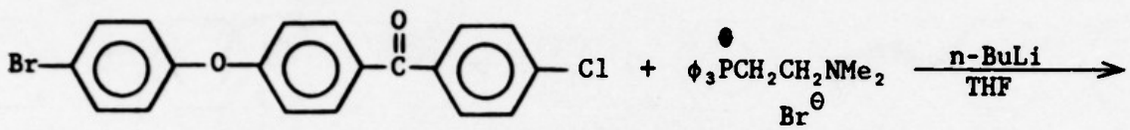
4 (96%, syrup)



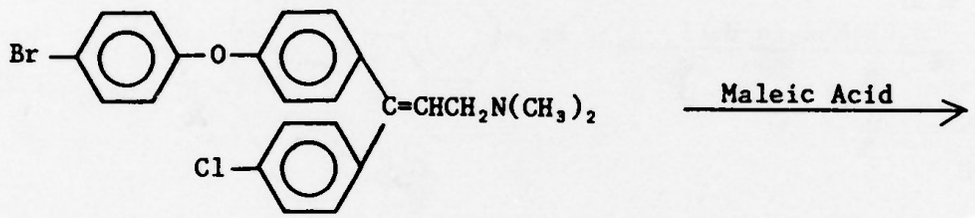
5, Free Base, ca. 100% oil.
5, Maleate Salt, 26%, SNL-128, BK21780, DJD-07-27.

CHART NO. 9

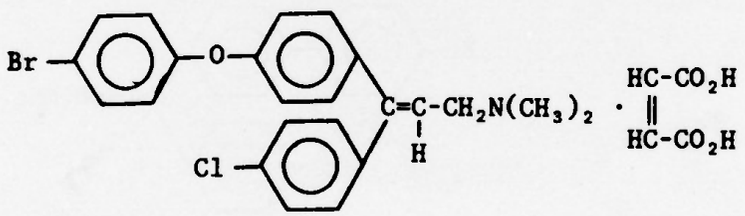
1-(4'-BROMOPHENOXY-4-PHENYL)-1-(4-CHLOROPHENYL)-3-DIMETHYLAMINOPROP-1-ENE MALEATE (SNL-129, BL22205)



(Compound 2, Chart No. 8)



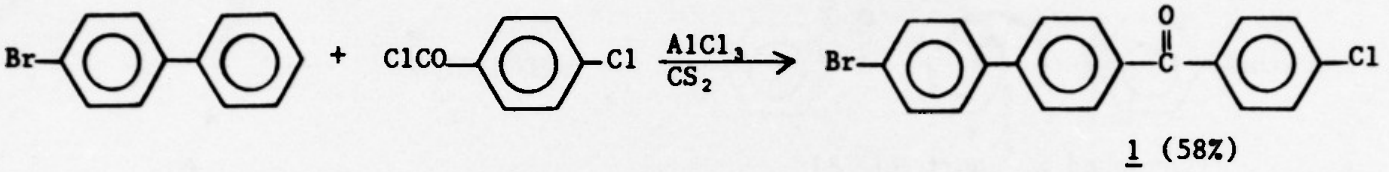
1 Free Base (42%)



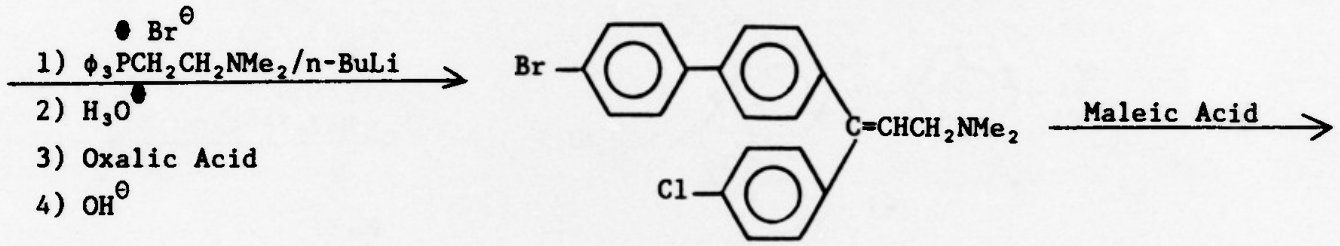
2 Maleate Salt (87%), SNL-129, BL22205, DJD-07-32

CHART NO. 10

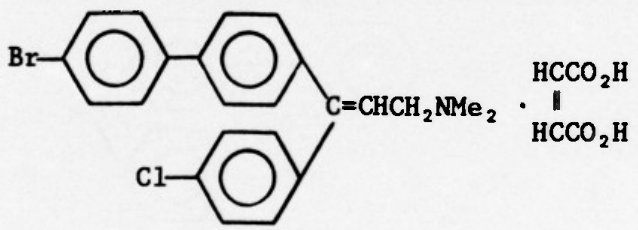
1-(4'-BROMO-4-BIPHENYLYL)-1-(4-CHLOROPHENYL)-3-DIMETHYLAMINOPROP-1-ENE MALEATE (SNL-130)



1 (58%)



2 (79%), Free base (oil).

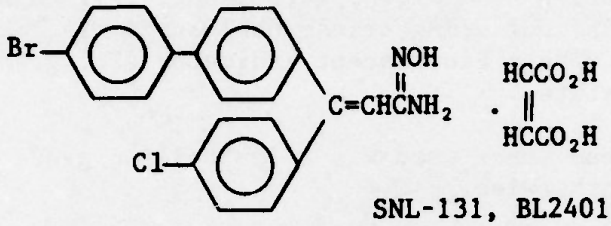


2 (97%), SNL-130, BL24003, DJD-07-44.
Wellcome Research Laboratories
Compound 353C as the tartrate salt.

4. WORK IN PROGRESS

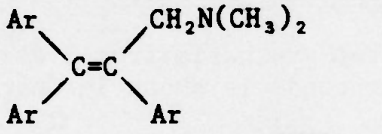
Work is in progress or planned on the three compounds discussed below.

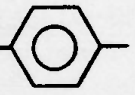
1) 1-(4'-Bromo-4-biphenylyl)-1-(4-chlorophenyl)-2-amidoximinoethylene Maleate

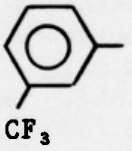


SNL-131, BL24012

The title amidoxime (SNL-131) was completed post-report. A 4.5 g sample was shipped September 11, 1986 as Code No. DJD-07-51. This is the amidoxime analog of the Wellcome Research Laboratories powerful trypanocide 353C against strains of Peruvian T. cruzi.



1) Ar = 

2) Ar = 

The above two compounds represent attempts to place three (identical) aryl groups on the ethylene portion of the molecule. These structures were discussed in our Proposal dated March 7, 1984 wherein they were designated compounds PC-26 and PC-27. Probe synthesis of compound 2 has been completed and scale-up is in progress. A literature survey for compound 3 or related structures has been completed and starting materials are on hand. The synthesis route will be essentially the same as for compound 5, section 3.5.

Note: These triaryl structures were successfully prepared post-report.

5. EXPERIMENTAL

All melting points and boiling points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 237B Spectrometer. Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, Indiana. Vapor phase chromatography was performed using an F and M Model 810 with a flame ionization detector. NMR spectra, when required, were determined on a Varian Model T60 Spectrometer. All thin layer chromatography was carried out using Brinkmann Instruments, Inc., 0.25 mm silica gel plates with a Fluorescent indicator (Polygram Sil G/UV_{254}) unless otherwise stated.

The petroleum ether used was a low boiling grade (bp 35-60°C) unless specified otherwise.

5.1 8-[(6-Amidoximinohexyl)amino]-6-methoxy-4-methylquinoline Succinate (SNL-118; BN BL12503)

5.2 8-[(6-Amidinohexyl)amino]-6-methoxy-4-methylquinoline Succinate (SNL-119; BN BL12790)

The three-step synthesis from 8-amino-6-methoxy-4-methylquinoline for both target compounds is shown in Chart No. 1.

8-[(6-Cyanohexyl)amino]-6-methoxy-4-methylquinoline (1): - A mixture of 8-amino-6-methoxy-4-methylquinoline (12 g, 64 mmol), 7-bromoheptanonitrile (15.5 g, 82 mmol) and diisopropylethylamine (12.5 g, 97 mmol) was stirred overnight under nitrogen at 125°C. The mixture was cooled to room temperature and partitioned between ethyl acetate (200 mL) and water (200 mL). The aqueous layer was extracted with ethyl acetate (2 x 200 mL). The extract was washed successively with 1% aq. sodium hydroxide (100 mL) and with water (2 x 200 mL), dried ($MgSO_4$), and concentrated (aspirator) to a greenish yellow solid. This material was dissolved in methylene chloride (∿ 70 mL) and chromatographed over silica gel (300 g packed in methylene chloride) and eluted with 2% ethyl acetate in methylene chloride. The product fractions were concentrated (aspirator) to a pale yellow solid, 17.5 g, which was dissolved in hot toluene (50 mL, ∿ 90°C). The solution was filtered (gravity), diluted with hot cyclohexane (150 mL) and allowed to cool to room temperature. The slurry was stirred overnight and filtered. The solid was washed with petr. ether (50 mL), air-dried, dried further at 55°C/1 mmHg for 2 h to give the title nitrile, 14 g (75%), pale-yellow crystalline solid, mp 94-96°C.

Anal. Calcd for $C_{18}H_{23}N_3O$ (297.40): C, 72.70; H, 7.79; N, 14.13. Found: C, 72.51; H, 7.94; N, 14.13.

8-[(6-Amidoximinohexyl)amino]-6-methoxy-4-methylquinoline Succinate (2): - A solution of hydroxylamine hydrochloride (18 g, 0.26 mol) in methanol (150 mL) was neutralized with a solution of potassium hydroxide (87.2% purity, 16.7 g, 0.26 mol) in methanol (70 mL) using phenolphthalein as indicator. The slurry was filtered (celite) and the collected salt was rinsed with methanol (30 mL). The nitrile 1 (7.5 g, 0.025 mol) was added to the filtrate. The mixture was stirred and heated (steam bath) overnight to give a solution which was concentrated (aspirator) to a slurry, ca. 40 mL. The slurry was cooled (ice bath) for 3 h and filtered. The solid product was washed with cold methanol (10 mL) and air-dried to a yellow solid, 8.9 g. This material was combined with a sample (1.15 g) from a trial run (from 1.0 g of nitrile 1) and slurried in water (20 mL) for 10 min. The solid was collected, washed with cold methanol (10 mL) and air-dried overnight to give a yellow solid, 8.3 g (88%), mp 119°C (dec) with shrinking at 113°C. The solid (8 g, 0.024 mol) was dissolved in methanol (60 mL, 50°C) and a warm solution (50°C) of succinic acid (2.87 g, 0.024 mol) in methanol (30 mL) was added. The solution was concentrated (aspirator) to ca. 50 mL to give a slurry which was cooled to 5°C and filtered. The solid was washed with cold methanol (15 mL) and air-dried to give a light-tan solid, 9.1 g, mp 140°C (dec). This material was dissolved in boiling ethanol (90 mL). The solution was filtered (gravity) and stirred at room temperature for 2 h to give a slurry. The solid was collected, washed with cold ethanol (10 mL), air-dried, then dried at 55°C/1 mmHg for 2 h to give the title intermediate 2, 8.7 g (64%), mp 142°C dec, cream-colored crystalline solid. A 5.0 g sample was shipped December 2, 1985 to Walter Reed as Code No. KW-08-188, BL12503, SNL-118.

Anal Calcd for $C_{22}H_{32}N_4O_6$ (448.52): C, 58.91; H, 7.19; N, 12.49. Found: C, 59.02; H, 7.14; N, 12.28.

8-[(6-Amidinohexyl)amino]-6-methoxy-4-methylquinoline Succinate (3): - The amidoxime succinate (2, 3.5 g) was dissolved in hot methanol (120 mL, 50°C). Raney nickel (14 g, wet) was added and the mixture was hydrogenated at 45 psig for 30 min. A total of 10.2 g (0.023 mol) of the amidoxime succinate was reduced in this manner. The reaction mixtures were filtered (celite) and the catalyst was washed with boiling methanol (3 x 300 mL). The filtrate was concentrated (aspirator) to ca. 100 mL, form a slurry which was heated (steam bath) to give a homogeneous solution. The solution was cooled to room temperature overnight. The solid was collected, washed with ethanol (10 mL) and air-dried to give a pale yellow crystalline solid, 6.3 g, mp 171-173°C. Concentration of the mother liquor gave a second crop, 1.1 g, mp 165-166°C. The second crop was recrystallized from methanol (12 mL) to give product, 0.7 g, mp 170-172°C. This material (0.7 g) was combined with the first crop (6.3 g) and dissolved in a boiling mixture of ethanol (90 mL) and water (10 mL). The solution was filtered (gravity), cooled to room temperature,

then refrigerated overnight. The solid was collected, washed with cold ethanol (10 mL), air-dried, then dried at 80°C/1 mmHg for 5 h to give the target amidine 3, 6.4 g (65%), as a pale-yellow crystalline solid, mp 171.5-173°C. A 6.0 g sample was shipped on January 8, 1986 to Walter Reed, Code No. KW-08-211B, BL12790, SNL-119.

Anal Calcd for $C_{22}H_{32}N_4O_5$ (432.52): C, 61.09; H, 7.46; N, 12.95. Found: C, 60.93; H, 7.48; N, 12.81.

5.3 1-(4-Methoxyphenyl)-1-(4'-methoxy-4-biphenylyl)-3-dimethylamino-prop-1-ene hydrochloride (SNL-120, BL18247)

The five-step sequence is shown in Chart No. 2.

4-Methoxy-4'-(4-methoxybenzoyl)biphenyl (1): - Anhydrous aluminum chloride (80 g, 0.6 mol) was added to a cold (-9°C) solution of 4-methoxybiphenyl (100 g, 0.54 mol) and 4-methoxybenzoyl chloride (100 g, 0.59 mol) in 1,1,2,2-tetrachloroethane (2 kg, 1.26 L). The reaction mixture, which exothermed to 0°C, was slowly warmed to room temperature over a period of 4 1/2 h, then stirred for 16 h. The mixture was cooled to ∿ 10°C and treated with dilute hydrochloric acid (2 L crushed ice containing 200 mL concd acid). The mixture was stirred for 30 min, warmed slowly to 40°C and stirred for 20 min. The clear organic layer was separated, cooled to room temperature, washed successively with dilute hydrochloric acid (concd acid-H_2O, 1:3, 800 mL), cold water (500 mL), 1 N sodium hydroxide (2 x 250 mL) and water (500 mL), then dried (Na_2SO_4).

A second run, same scale, was worked up separately. The two runs were combined and dried further (1.0 mmHg; water bath, 50-70°C). The residue was treated with hot benzene (300 mL) and the mixture was cooled slowly to 45°C. The title compound was collected by filtraiton, washed with benzene (4 x 50 mL), followed by hexanes (4 x 250 mL), and air-dried (16 h) to give the title intermediate, 65 g (19%), mp 208-211°C.

Using the procedure described above, a total of 124.6 g of crude title compound was prepared. This material was dissolved in hot chloroform (3.2 L), filtered and the volume was reduced to ca. 2.5 L. The white solid was collected, washed with hexanes (2 x 500 mL) and dried (80°C/0.3 mmHg/1 h) to give pure title compound, 103.5 g, mp 211-213°C. Rework of mother liquor gave additional pure title compound, 14.9 g, mp 210-212°C. The combined yield of intermediate 1 was 118 g (17%).

Anal Calcd for $C_{21}H_{18}O_3$ (318.35): C, 79.22; H, 5.70. Found: C, 79.03; H, 5.69.

3-Hydroxy-3-(4'-methoxy-4-biphenylyl)-3-(4-methoxyphenyl)propionitrile (2): - This compound was prepared as described earlier from a diphenyl ether analog ((2) p. 44). A mixture of sodium amide (11.6 g, 0.3 mol), acetonitrile (15 mL, 11.8 g, 0.29 mol) and dry benzene (1 L) was heated to reflux for 15 min. The mixture was cooled to 50°C and intermediate 1 (60 g, 0.19 mol) and 250 mL dry benzene were added. The mixture was refluxed for 6 min and additional acetonitrile (20 mL) and benzene (400 mL) was added. The mixture was refluxed for 13 min, cooled and wshed with cold water (750 mL). The organic layer was separated an the aqueous layer was extracted with benzene (2 x 250 mL). The organic layers were combined, dried (Na_2SO_4) and concd to give crude title compound, 66 g.

A total of 107 g of crude title compound, prepared in this way from 100 g of intermediate 1, was purified by column chromatography over EM silica gel (1.5 kg), eluting with a mixture of hexane and methylene chloride (2:8, 1 L, 1:9, 1 L) to remove unreacted ketone 1 (11.8 g). The product (83 g) was eluted with ethyl acetate and dissolved in hot benzene (850 mL). The solution was filtered and the volume was reduced to 500 mL. Hexanes (1 L) was added and the mixture was filtered. The product was washed with hexanes (500 mL) and dried (50°C/0.3 mmHg/2 h) to give pure title compound, 82 g (82%), mp 138-140°C.

Anal Calcd for $C_{23}H_{21}NO_3$ (359.40): C, 76.86; H, 5.89; N, 3.90. Found: C, 76.68; H, 5.68; N, 3.87.

3-Hydroxy-3-(4'-methoxy-4-biphenylyl)-3-(4-methoxyphenyl)propylamine (3): - A solution of intermediate 2 (30 g, 0.083 mol) in dry tetrahydrofuran (250 mL) was added to a suspension of lithium aluminum hydride (12 g, 0.31 mol) in dry anhyd. ether (350 mL). The mixture was held at 5°C-7°C for 25 min, warmed to room temperature, stirred for 1 h and cooled to 10°C. Water (25 mL) was added, followed by 15% aq. sodium hydroxide (25 mL) and by water (25 mL). The mixture was filtered (celite), the inorganic residue was slurried with methylene chloride (500 mL) and refiltered. The filtrate was concd to dryness, dissolved in methylene chloride (500 mL) and dried (Na_2SO_4). The mixture was concentrated to give crude title compound, 25.5 g (84%), mp 148-150°C, as a white solid.

An analytical sample, prepared by recrystallization from acetonitrile, had mp 150-152°C.

Anal. Calcd for $C_{23}H_{25}NO_3$ (363.44): C, 76.00; H, 6.93; N, 3.85. Found: C, 75.95; H, 6.77; N, 4.00.

Using the procedure described above, a total of 34 g of the crude title compound was prepared for use in the next step.

1-(4-Methoxyphenyl)-1-(4'-methoxy-4-biphenylyl)-3-amino-1-propene (4): - A mixture of intermediate 3 (17 g, 0.047 mol), acetic acid (170 mL) and concd hydrochloric acid (68 mL) was heated (steam bath) for 35 min and concentrated to dryness (vacuum pump, 10 min). The residue was dissolved in warm (75°C) deionized water (1.5 L) to give a clear yellow solution. The solution was adjusted to pH 14 with 2 N NaOH (480 mL) while maintaining the temperature between 10-15°C. The off-white solid was collected, washed with water (4 x 150 mL) to pH 7 and dissolved in methylene chloride (600 mL). The organic layer was dried (K_2CO_3), concentrated to near dryness and diltued with hexanes (200 mL). The beige solid was collected by filtration and dried (25°C, 2 h) to give the title compound, 12.9 g (80%), mp 113-115°C.

An analytical sample was prepared by recrystallization from heptanes, mp 115-118°C.

Anal Calcd for $C_{23}H_{23}NO_2$ (345.42): C, 79.96; H, 6.71; N, 4.06. Found: C, 79.71; H, 6.65; N, 4.32.

Using the procedure described above, a total of 25.2 g of the title compound was prepared and used as such in the next step.

1-(4-Methoxyphenyl)-1-(4'-methoxy-4-biphenylyl)-3-dimethylamino-prop-1-ene Hydrochloride (5): - A 37% aq. formaldehyde (3 mL, 0.037 mol), sodium cyanoborohydride (1.3 g, 0.02 mol) and acetic acid (0.8 mL) were added over 30 seconds to a cold (3°C) solution of intermediate 4 (2 g, 5.8 mmol) in acetonitrile (100 mL). The temperature rose to 7°C and the mixture was stirred for 3 min. Cold water (200 mL) and 2 N NaOH (15 mL, pH 14) were added. The product was extracted with ether (250 mL), dried (K_2CO_3) and concentrated to give an oily residue, 3 g which was redissolved in anhyd ether (150 mL) and treated with a solution of anhyd oxalic acid (1.3 g, 0.014 mol) in anhyd ether (50 mL). The oxalate salt was collected, washed with anhyd ether (100 mL) and dissolved in methylene chloride (150 mL). The solution was washed with 2 N NaOH solution (150 mL), water (100 mL), dried (K_2CO_3) and concentrated to a thick yellow oil, 2.1 g. The oil was extracted with hot petr. ether (6 x 25 mL). The extract was concentrated to give crude title compound, free base, 1.2 g. In this manner, a total of 18 g of intermediate 4 was converted to the crude free base, 10 g.

This material (10 g) was purified by column chromatography over silica gel (EM, 100 g), eluting with methylene chloride and methanol. The appropriate 25 mL fractions were combined and concd to give purified title compound, free base, 6.2 g. The free base was dissolved in ethanol (20 mL) and acidified to pH 1 with ethanolic hydrogen chloride (3 mL, 10.5 M). The solution was diluted with anhyd ether (200 mL). The resulting solid was collected by filtration, washed with anhyd ether (2 x 50 mL) and dried (25°C, 1 h) to give purified title compound as the hydrochloride salt. This salt was dissolved in water (120 mL),

washed with ether and charcoaled. The solution was adjusted to pH 14 with 2 N sodium hydroxide (30 mL). The free base was extracted with ether (2 x 250 mL). The extract was washed with cold water (100 mL), dried (K_2CO_2), and concentrated to an oily residue. The residue was dissolved in hot hexanes (150 mL), filtered (celite) and concentrated to give pure title compound, free base, 5.2 g. The pure free base was dissolved in ethanol (20 ML), acidified to pH 1, filtered and diluted with anhyd ether (150 mL) to give pure title compound as a light-yellow solid, 5 g (23%), mp 185-190°C, shrinks at 150-155°C. A 4.5 g sample was shipped January 23, 1986 as DJD-06-210.

Anal. Calcd for $C_{25}H_{27}NO_2 \cdot HCl$ (409.95): C, 73.24; H, 6.88; Cl, 8.65; N, 3.42. Found: C, 72.98; H, 6.95; Cl, 8.54; N, 3.43.

5.4 1-(4'-Methoxy-4-biphenylyl)-1-(4-methoxyphenyl)-2-amidoximinoethylene Maleate (SNL-121; BK40799)

The synthesis sequence is shown in Chart No. 3.

3-(4'-Methoxy-4-biphenylyl)-3-(4-methoxyphenyl)acrylonitrile (1): Phosphorous pentoxide (30 g) was added to a warm soln of the 3-hydroxypropionitrile (compound 2, section 5.3 above; 20 g, 0.056 mol) in benzene (800 mL). The mixture was refluxed with stirring for 10 min (no starting material by TLC). The yellow soln was decanted and the dark gummy residue was washed with hot benzene (3 x 50 mL). The combined benzene soln was charcoaled (Norit), filtered (celite) and concd to dryness (aspirator). The crystalline residue (mp ca. 102°C) was redissolved in xylene (400 mL). A crystal of iodine was added and the soln was refluxed for 4 h. The solvent was evaporated (aspirator) and the residue dried (0.3 mmHg, 50°C) to remove traces of xylene. The solid residue was dissolved in hot benzene (100 mL) and the clear soln was diluted with petr ether (bp 30-60°C, 150 mL). After cooling, crystalline product 1 was separated, washed with petr ether and dried (0.3 mmHg, 50°C) to give 15.2 g (80%), mp 105-107°C. This product was identical (NMR, TLC) with the analytical sample obtained from the probe run (anal. below).

Anal. Calcd for $C_{23}H_{19}NO_2$ (341.40): C, 80.91; H, 5.61; N, 4.10 Found: C, 80.74; H, 5.49; N, 4.30.

1-(4'-Methoxy-4-biphenylyl)-1-(4-methoxyphenyl)-2-amidoximinoethylene Maleate (2, SNL-121, BK40799): - A hot soln of hydroxylamine hydrochloride (8.2 g, 0.12 mol) in methanol (60 mL) was added to a warm (50°C) soln of the nitrile 1 (15 g, 0.044 mol) in pyridine (150 mL). Sodium bicarbonate (9.9 g, 0.12 mol) was added portionwise (foaming). The mixture was refluxed for 24 h (50% starting material present by TLC). More hydroxylamine hydrochloride (8.2 g, 0.12 mol) and sodium bicarbonate (9.9 g, 0.12 mol) were added and the mixture

was refluxed for 24 h (reaction still not complete by TLC). After cooling, sodium chloride was separated and washed with methanol (2 x 50 mL). The filtrate and methanolic washings were combined and evaporated to dryness. The resulting foam was azeotroped with ethanol (100 mL) to remove residual pyridine. The foamy residue was dissolved in methylene chloride (300 mL) and the soln was washed with water (3 x 50 mL). The organic layer was dried ($MgSO_4$), charcoaled (Norit) and the solvent was evaporated (aspirator). The solid residue was dissolved in hot ethanol (90 mL), and seeded with an authentic sample of the title free base obtained from a probe run. After cooling (ice-bath), pure amidoxime 2 free base was separated, washed with cold ethanol and petr ether. After drying (0.3 mmHg, 25°C) pure amidoxime 2 free base was obtained, 6.2 g (38%), mp 114-117°C.

Anal. Calcd for $C_{23}H_{22}N_2O_3$ $0.3H_2O$ (380.44): C, 72.61; H, 5.90; N, 7.36. Found: C, 72.56; H, 5.85; N, 7.20.

Conversion of the Free Base to the Maleate Salt 2 (SNL-121): - The amidoxime free base 2 (6 g, 0.016 mol) was dissolved in hot ethanol (60 mL) and an ethanolic soln of maleic acid (2 g, 0.017 mol in 10 mL of ethanol) was added in one portion. The clear soln was concd to dryness. The solid residue was dissolved in boiling acetonitrile (50 mL). The soln was filtered, diluted with ether (50 mL) and cooled. Crystalline maleate salt 2 was separated, washed with ether and dried to give pure title target salt 2, 5.6 g (69%), mp 150-153°C. A 5 g sample was shipped to WRAIR as Code No. AM-04-28, BK40799 on March 31, 1986.

Anal. Calcd for $C_{22}H_{22}N_2O_3$ $C_4H_4O_4 \cdot 0.3H_2O$ (496.23): C, 65.35; H, 5.40; N, 5.65. Found: C, 65.55; H, 5.45; N, 5.82.

5.5 1-(3'-Trifluoromethylphenoxy-4-phenyl)-1-(4-trifluoromethylphenyl)-3-dimethylaminoprop-1-ene Maleate (6, SNL-122, BL19333)

5.6 1-(3'-Trifluoromethylphenoxy-4-phenyl)-1-(4-trifluoromethylphenyl)-3-aminoprop-1-ene Maleate (5a, SNL-123, BL19324)

The synthesis sequence for the two compounds is shown in Chart No. 4.

4-(3'-Trifluoromethylphenoxy)benzaldehyde (1): - The potassium salt of 3-trifluoromethylphenol was prepared by adding a soln of 3-trifluoromethylphenol (140 g, 0.86 mol) in methanol (200 mL) to a warm (40°C) soln of powdered potassium hydroxide (56 g, 86% pure, 0.86 mol) in methanol (500 mL). The yellow-orange soln was stirred for 1 h at room temp and cond to dryness (50°C, aspirator). The potassium salt was dried at 40-50°C at 1 mmHg for 3 h and then

overnight at room temp. The dried salt was mixed with 4-fluorobenzaldehyde (96.5 g, 0.78 mol) in dimethylformamide (550 mL) under a nitrogen atmosphere. the mixture was refluxed for 2 h (oil bath, 170-180°C) and cooled to 50°C. DMF was largely removed at 45-55°C, 1 mmHg. The residue was stirred with a mixture of ether (1 L) and water (1 L). the layers were separated and the aq layer was extracted with ether (500 mL). the ether layer was dried (Na_2SO_4) with charcoaling. The soln was filtered (celite) and concd to give crude title compd, 190 g. This material was chromatographed in two equal portions over EM silica gel (850 g), eluting initially with petr ether (2.5 L, discarded). Elution with ether-petr ether (1:9, 4 L and 1:7, 4 L) gave pure title compd. The eluates were concd to dryness and the residue was distilled. The fraction, bp 124-126°C/0.1 mmHg, was collected as a colorless oil which solidified upon cooling to room temp, gave pure title benzaldehyde 1, 175 g (85%), mp 45-48°C.

Anal. Calcd for $C_{14}H_9F_3O_2$ (266.21): C, 63.16; H, 3.41; F, 21.41. Found: C, 63.04; H, 3.44; F, 21.59.

4-Trifluoromethyl-4-(3-trifluoromethylphenoxy)benzophenone (2): - Magnesium turnings (18.5 g, 0.74 mol) were washed with anhyd ether (3 x 150 mL) and dried (140°C) prior to use. A mixture of the turnings, 4-bromobenzotrifluoride (2 g, 0.009 mol) and iodine (0.35 g) in anhyd ether (110 mL) was stirred at reflux to initiate the reaction as evidenced by the disappearance of the iodine color. The remaining 4-bromobenzotrifluoride (97 g, 0.43 mol) in anhyd ether (500 mL) was added over 45 min under nitrogen at reflux. The soln was refluxed for 30 min and transferred to an addition funnel via cannulae using positive nitrogen pressure.

The 4-trifluoromethylphenylmagenesium bromide was added over 20 min to a soln of phenoxybenzaldehyde 1 (85 g, 0.32 mol) in anhyd ether (500 mL) while maintaining the temp between 40-50°C. The mixture was refluxed for 45 min, cooled to room temp and poured carefully into cold dil hydrochloric acid (concd acid-water, 16:84). The organic layer was washed successively with 500 mL each of cold water, satd sodium bicarbonate soln and with cold water, dried (Na_2SO_4) with charcoaling and filtered (celite). The filtrate was concd to give the intermediate diarylcarbinol, 130 g, which was purified by column chromatography over EM silica gel (900 g). The column was eluted with petr ether (2 L) and with 5% ether-petr ether (1 L); both eluates were discarded. Elution with 10% ether-petr ether (1 L) and with 15% ether-petr ether (1 L) gave slightly impure product (38 g). Elution with ether-petr ether (1:4, 4 L) gave pure title diaryl carbinol 2, 86 g.

The reaction was repeated to give additional impure product, 50 g, and pure product, 71 g. The impure material from both runs (88 g) was purified again as above to give pure diarylcarbinol, 57 g.

From both experiments a total of 214 g of pure diarylcarbinol (81%) was isolated and used directly in the next step.

Oxidation of the Diarylcarbinol to the Diaryl Ketone: - Glacial acetic acid (24 mL) and concd sulfuric acid (35 mL) were added to a 22.3% aq sodium dichromate soln (130 mL) at room temp. The mixture exothermed to 48°C and was cooled to 16°C. A soln of the diarylcarbinol (78.5 g, 0.19 mol) in benzene (800 mL) was added over 1 h while maintaining the temp between 22°C to 26°C, then stirred for 20 min. The layers were separated; the aq layer was diluted with water (200 mL) and extracted with benzene (200 mL). The combined benzene layers were washed successively with water (1 L), satd aq sodium bicarbonate (2 x 500 mL) and water (2 x 300 mL) and dried (Na_2SO_4) with charcoaling. The soln was filtered (celite), concd to dryness and triturated with hexanes (350 mL). The white solid was collected and dried (25°C, 0.3 mmHg) to give crude title compound, 62 g, mp 65-67°C.

The run was repeated in the same manner to give additional crude compd, 60 g. The combined crudes (122 g) were dissolved in hot benzene (1.2 L), charcoaled and filtered (celite). The soln volume was reduced to ca. 1 L and diluted with hexanes (200 mL). The white solid was collected and dried (25°C, 18 h) to give pure title ketone 2, 84 g (61%), mp 69-71°C.

Anal. Calcd for $C_{21}H_{12}F_6O_2$ (410.31): C, 61.47; H, 2.95; F, 27.78. Found: C, 61.61; H, 2.72; F, 27.88.

3-Hydroxy-3-(3'-trifluoromethylphenoxy-4-phenyl)-3-(4-trifluoromethylphenyl)propionitrile (3): - A mixture of sodium amide (6 g, 0.154 mol), acetonitrile (10 mL, 7.86 g, 0.19 mol) and dry benzene (300 mL) was refluxed 10 min and cooled to 50°C. A soln of intermediate 2 (45 g, 0.11 mol) in benzene (225 mL) was added at once and the soln was refluxed for 5 min. Additional acetonitrile (10 mL) was added and heating was continued for 15 min. The mixture was cooled to room temp and poured into cold water (225 mL). The organic layer was separated, washed with water (250 mL), dried (Na_2SO_4) with charcoaling and filtered (celite). The filtrate from two such runs were combined and concd to dryness to give a brown oil, 96.5 g, which was purified by column chromatography over EM silica gel (1 kg). Elution with ether-petr ether (1:20, 4 L; 1:9, 2 L; 1.5:8.5, 2 L) removed unreacted ketone (22 g). Elution with ether-petr ether (1:5, 2 L) gave slightly impure nitrile 3, 8 g. Elution with ether-petr ether (3:7, 2 L and 1:1, 2 L ether) gave pure title compd 3, 54 g (72%) as a light-yellow oil.

3-Hydroxy-3-(4-trifluoromethylphenyl)-3-(3'-trifluoromethylphenoxy-4-phenyl)propylamine (4):- A soln of intermediate 3 (54 g, 0.12 mol) in dry tetrahydrofuran (550 mL) was added over 40 min to a suspension of lithium aluminum hydride (19.8 g, 0.52 mol) in anhyd ether (800 mL) while maintaining the temp between 6° to 9°C. Additional dry tetrahydrofuran (250 mL) was added and the mixture was warmed slowly to room temp, stirred for 90 min and cooled to 10°C. Water (50 mL), 15% aq sodium hydroxide (50 mL) and water (50 mL) were added and the mixture was stirred for 15 min and filtered (celite). The inorganic residue was slurried with dichloromethane (1 L) for 10 min and the slurry was filtered. The combined filtrate was dried (Na_2SO_4), filtered and concd to dryness. The residue was dried (50-60°C, 0.1 mmHg, 1 h) to give crude title compd 4, 51 g (94%), which was used directly in the next step.

1-(3'-Trifluoromethylphenoxy-4-phenyl)-1-(4-trifluoromethylphenyl)-3-aminoprop-1-ene (5) and the Maleate Salt (5a): - A soln of intermediate 4 (26.5 g, 0.056 mol) in acetic acid (250 mL) was mixed with concd hydrochloric acid (100 mL), heated (steam bath) for 35 min and concd to dryness (2 mmHg, 10 min). The residue was dissolved in warm (50°C) water (500 mL). The soln was cooled to 10°C and the pH was adjusted to ca. 14 with 15% aq NaOH (400 mL). The product was extracted with ether (1 L) and the extract was washed with 2 N aq NaOH (250 mL), water (250 mL) and dried (K_2CO_3) with charcoaling. The ether extract was filtered (celite), combined with the filtrate from another identical experiment, and concd to dryness to give crude title compd, 48 g. This material was purified by column chromatography over EM silica gel (500 g). Elution with chloroform (1 L), 1% MeOH-$CHCl_3$ (1 L); 2.5% MeOH-$CHCl_3$ (1 L) removed impurities. Elution with 3.5% MeOH-$CHCl_3$ (1 L) gave slightly impure title compd, 26 g. Elution with 5% MeOH-$CHCl_3$ (1 L) and 7.5% MeOH-$CHCl_3$ (1 L) gave purified title compd, 17.9 g (36.5%). The slightly impure title compd (26 g) was purified again in the same manner to give additional pure title compd, 20.7 g (42%). The overall yield of pure title free base 5 was 38.6 g (79%). As described below, a portion of this, 12.2 g, was converted to the maleate salt 5a (SNL-123) and the balance was converted to target compd 6, SNL-122.

Conversion of the Free Base 5 to the Maleate Salt (5a, SNL-123, BL19324): - A soln of maleic acid (2.9 g, 0.025 mol) in methanol (15 mL) was added to a soln of the free base 5 (12.2 g, 0.028 mol) in anhyd ether (150 mL). The mixture was stirred for 30 min, concd to dryness and dried (30-40°C, 0.1 mmHg, 10 min). The resulting foam was triturated with anhyd ether (180 mL), filtered, washed with anhyd ether (2 x 100 mL) and with petr ether (100 mL) and dried (25°C, 0.3 mmHg, 18 h) to give the title maleate salt, 12.9 g (93%), as an off-white solid, mp 120-124°C. A sample, 10.0 g, was shipped to WRAIR on April 14, 1986 as Code No. DJD-06-270; BN BL19324.

Anal. Calcd for $C_{27}H_{21}F_6NO_5$ (553.45): C, 58.59; H, 3.82; F, 20.60; N, 2.53. Found: C, 58.42; H, 3.95; F, 20.66; N, 2.69.

1-(3'-Trifluoromethylphenoxy-4-phenyl)-1-(4-trifluoromethylphenyl)-3-dimethylaminoprop-1-ene Maleate (6, SNL-122, BL19333): - A 37% aq formaldehyde (12 mL, 0.15 mol), sodium cyanoborohydride (5.5 g, 0.087 mol) and acetic acid (4.1 mL) were added rapidly to a cold (3°C) soln of intermediate free base 5 (2.93 g, 6.69 mmol) in HPLC-grade acetonitrile (200 mL exotherm to 12°C). The mixture was stirred for 10 min (+5°C); cold water (300 mL) and 2 N NaOH (100 mL) were added. The mixture was extracted with ether (600 mL). The extract was combined with the extract from a 4.43 g run (intermediate 5) and concd to dryness. The yellow residue was dissolved in ether (300 mL) and washed with satd sodium chloride (2 x 300 mL). The ether soln was dried (K_2CO_3), filtered and a soln of maleic acid (2.6 g, 0.022 mol) in methanol (10 mL) was added to the filtrate. The mixture was stirred, concd to dryness and the residue was triturated thoroughly with anhyd ether (150 mL). The solid was collected, washed with anhyd ether (2 x 50 mL) and with petr ether (50 mL) and air-dried to give the maleate salt, 6.6 g. In this manner, a total of 15 g (34.29 mol) of intermediate 5 was converted to crude title maleate salt, 13.4 g. To purify this material, this crude salt was reconverted to the free base and chromatographed as described in the next paragraph.

The maleate salt (13.4 g) was stirred with methylene chloride (500 mL) and 2 N NaOH (300 mL). The organic layer was separated, washed with 2 N NaOH (200 mL) and with water (3 x 250 mL, pH 7) and dried (K_2CO_3) with charcoaling. The soln was filtered (celite) and concd to the free base as an oil which was chromatographed over J.T. Baker silica gel (75 g). Eluting with methylene chloride (250 mL) removed some impurities. Elution with MeOH:CH_2Cl_2 (1:20, 250 mL, 1:10, 250 mL) gave pure title compound 6 free base, 7.94 g (50%), as a clear light yellow oil.

Conversion to Maleate Salt (6, SNL-122): - A soln of maleic acid (1.84 g, 0.016 mol) in methanol (15 mL) was added to an ether soln (325 mL) of the free base (7.94 g, 0.017 mol). The mixture was stirred for 1 h and filtered. The white solid was washed with anhyd ether (2 x 100 mL) followed by petr ether (100 mL) and dried (25°C, 0.3 mmHg, 20 h) to give pure title maleate salt 6, 8.2 g (83% from 6, free base; 44% from 5), mp 142-145°C. A 7.5 g sample was shipped to WRAIR on April 14, 1986 as Code No. DJD-06-268, BL19333.

Anal. Calcd for $C_{29}H_{25}F_6NO_5$ (581.5): C, 59.89; H, 4.33; F, 19.60; N, 2.41. Found: C, 59.92; H, 4.34; F, 19.41; N, 2.67.

5.7 1-(3'-Trifluoromethylphenoxy-4-phenyl)-1-(4-trifluoromethylphenyl)-2-amidoximinoethylene Maleate (SNL-124, BL19315)

The synthesis sequence is shown in Chart No. 5.

3-(3'-Trifluoromethylphenoxy-4-phenyl)-3-(4-trifluoromethylphenyl)acrylonitrile (1): - A soln of the corresponding propionitrile (intermediate 3 from Chart No. 4, 10.0 g, 0.022 mol) in benzene (250 mL) was heated to 75°C and treated with phosphorus pentoxide (12.0 g). The mixture was heated to reflux with stirring for 15 min. The reaction mixture was cooled to room temp and the benzene supernate was decanted from a brown gum. The gum was triturated with benzene (2 x 10 mL) and the benzene layers were combined, washed with water (20 mL) and concd to give intermediate 1, 10.0 g, as a syrup.

1-(3'-Trifluoromethylphenoxy-4-phenyl)-1-(4-trifluoromethylphenyl)-2-amidoximinoethylene Maleate (2, SNL-124, BL19315): - Intermediate 3 (10.0 g, 0.023 mol) and hydroxylamine hydrochloride (20.5 g, 0.029 mol) were dissolved in a mixture of pyridine (43 mL) and methanol (92 mL) and treated in portions with sodium bicarbonate (24.3 g, 0.029 mol). The mixture was heated at reflux overnight. The inorganic salts were removed by filtration and the filtrate was concd to a syrup. The syrup was dissolved in methylene chloride, washed with water (2 x 50 mL) and concd to a syrup. The syrup was dissolved in a soln of maleic acid (3.11 g, 0.029 mol) in methanol (100 mL). The soln was concd to a syrup and treated with ether (100 mL). The mixture was allowed to stand at room temp for 2 h. The crystalline material was removed by filtration and washed with ether (2 x 25 mL). The filter cake was slurried in water (70 mL) for 30 min, collected by filtration, washed with water (2 x 10 mL) and air-dried overnight to give 6.30 g (47%) of product. The product was dissolved in a boiling mixture of ethanol (25 mL) and water (38 mL). The soln was filtered, allowed to cool to room temp over 2 h and then stored at 5°C overnight. The solids were removed by filtration, washed with aq ethanol (40%, 10 mL) and dried at 80°C/0.01 mmHg for 1 h to give the title compd 2; 5.85 g (44% from the starting propionitrile), as a cream-colored crystalline solid, mp 150-152°C. A 5.0 g sample was shipped to WRAIR on April 14, 1986 as Code No. RK-04-154, BL19315.

Anal. Calcd for $C_{27}H_{20}F_6N_2O_6$ (582.46): C, 55.68; H, 3.46; F, 19.57; N, 4.81. Found: C, 55.48; H, 3.35; F, 19.32; N, 4.96.

5.8 1-Bis(4-methylthiophenyl)-3-dimethylaminoprop-1-ene Maleate (6, SNL-125, BL20336)

5.9 1-Bis(4-methylthiophenyl)-3-aminoprop-1-ene Maleate (5a, SNL-126, BL20345)

The sequence to the two title compounds is shown in Chart No. 6.

4-(Methylthio)benzoyl chloride (1): - Phosphorus pentachloride (50 g, 0.24 mol) was added to 4-(methylthio)benzoic acid (39 g, 0.23 mol) and the mixture was refluxed (heating mantle) for 75 min. Phosphorus oxychloride was removed by distillation (aspirator) and the residue was codistilled with toluene (2 x 30 mL). The residue was distilled and the fraction with bp 148-150°C/5 mmHg was collected as light-yellow oil which solidified at room temp to give pure title compd, 41.2 g (95%), mp 50-53°C, as a off-white solid.

4,4'-Bis(thiomethyl)benzophenone (2): - Anhyd aluminum chloride (52 g, 0.39 mol) was added in three portions to a cold soln of 4-(methylthio)benzoyl chloride (41.2 g, 0.22 mol) in thioanisole (82 g, 0.66 mol). The temp was maintained at -9°C but exothermed to 25°C. The mixture was maintained at 10-15°C for 30 min and crushed ice (1 L) was added to decompose the complex. The mixture was stirred for 20 min, filtered and the off-white solid was washed with deionized water (2 x 250 mL). The solid was dissolved in dichloromethane (500 mL). The soln was washed with deionized water (2 x 150 mL), dried (Na_2SO_4), concd to dryness and codistilled with hexanes(150 mL). The resulting solid was triturated with warm (40°C) ethanol (150 mL), collected by filtration, washed with petr ether (2 x 100 mL) and dried (25°C, 1 h) to give crude title compd 2, 51 g, mp 123-125°C.

Using the same procedure a total of 64 g of crude compd from 51.2 g of compd 1 was prepared which was dissolved in refluxing ethanol (850 mL). The soln was filtered (celite), cooled to room temp and stirred for 30 min. The light-yellow solid was collected, washed with petr ether (3 x 250 mL) and dried (60°C, 0.3 mmHg, 1 h) to give pure title compd 2, 48.3 g (63%), mp 124-126°C; lit. 125°C (9).

3-Hydroxy-3-bis(4-methylthiophenyl)propionitrile (3): - A mixture of sodium amide (11.2 g, 0.29 mol), acetonitrile (25 mL, 19.6 g, 0.48 mol) and dry benzene (630 mL) was refluxed for 10 min and cooled to 50°C. Intermediate ketone 2 (41.4 g, 0.15 mol) in benzene (300 mL) was added and the mixture was heated to reflux. Acetonitrile (25 mL, 19.6 g, 0.48 mol) and benzene (300 mL) were added. The mixture was refluxed 8 min, cooled to room temp (1 h) and mixed with cold water (500 mL). The organic layer was separated and washed with cold water (500 mL), dried (Na_2SO_4) and concd to dryness to give a crude product mixture, 45 g.

This material (45 g) was mixed with product (7.7 g from 6.7 g of compd 2) from another run and purified by column chromatography to give recovered starting ketone, 9 g, and crude title compound, 44 g. The latter was dissolved in hot benzene (500 mL), charcoaled, filtered (celite). The volume was reduced to 300 mL, diluted with n-hexanes (250 mL) and stirred for 30 min. The white solid was collected, washed with hexanes (2 x 250 mL) and dried (80°C, 0.3 mmHg, 4 h) to give pure title compd 3, 37 g (82%), mp 95-97°C.

Anal. Calcd for $C_{17}H_{17}NOS_2$ (315.45): C, 64.72; H, 5.43; N, 4.44; S, 20.33. Found: C, 64.72; H, 5.56; N, 4.54; S, 20.18.

3-Hydroxy-3-bis(4-methylthiophenyl)propylamine (4): - A soln of the hydroxynitrile 3 (19 g, 0.06 mol) in dry tetrahydrofuran (450 mL) was added over 35 min to a suspension of lithium aluminum hydride (10 g, 0.26 mol) in dry anhyd ether (500 mL) while maintaining the temp between 2° to 9°C. Dry tetrahydrofuran (500 mL) was added and the mixture was warmed slowly to room temp and stirred for 1 h. Water (25 mL), 15% NaOH soln (25 mL) and water (25 mL) was added while keeping the mixture at ca. 10°C. The mixture was filtered and the resulting inorganic residue was slurried with dichloromethane (500 mL) and filtered. The combined filtrate was dried (Na_2SO_4), filtered, concd to dryness (rotavapor) and the residue was triturated with hexanes (150 mL). The solid was collected and dried (25°C, 0.3 mmHg, 16 h) to give the title compd 4, 16.9 g (88%), mp 97-100°C.

An analytical sample was prepared by purifying the above product (0.8 g) by column chromatography over silica gel (10 g, J.T. Baker). The collected product (0.45 g) was recrystallized from ether-petr ether (1:1) to give the sample, 0.3 g, mp 101-103°C.

Anal. Calcd for $C_{17}H_{21}NOS_2$ (319.45): C, 63.91; H, 6.62; N, 4.38; S, 20.07. Found: C, 63.75; H, 6.82; N, 4.57; S, 19.83.

1-Bis(4-methylthiophenyl)-3-aminoprop-1-ene (5): - A soln of the hydroxyamine 4 (16 g, 0.05 mol) in warm (60°C) acetic acid (160 mL) was mixed with concd HCl (64 mL) and heated (steam bath) for 25 min. The mixture was concd to dryness (aspirator, steam bath). The residue was dissolved in warm (60°C) deionized water (300 mL). The soln was cooled to 10°C, basified to pH 14 with 15% aq NaOH (300 mL) and extracted with dichloromethane (500 mL). The extract was washed with deionized water (150 mL), dried (K_2CO_3) and concd to dryness. The thick oil was dried overnight (room temp, 0.5 mmHg) to give the title compd crude free base 5 as a beige solid, 13.5 g (89%), mp 52-55°C. As discussed below, a portion (4.30 g) of this was chromatographed.

Conversion to the Maleate Salt (5a, SNL-126, BL20345): - The crude free base 5 (4.3 g) was purified by column chromatography over silica gel (80 g, J.T. Baker). Elution with dichloromethane (500 mL) and 1% MeOH (500 mL) removed the faster-moving impurities. Successive elution with 2% MeOH (500 mL), 4% MeOH (500 mL); 6% MeOH (250 mL) and 8% aq MeOH (250 mL) gave purified free base, 3.56 g. This material (3.56 g, 0.012 mol) was dissolved in anhyd ether (300 mL) and mixed with a soln of maleic acid (1.24 g, 0.011 mol) in methanol (10 mL). The mixture was stirred at room temp for 1 h and filtered. The maleate salt was washed with anhyd ether (2 x 100 mL) and with petr ether (100 mL) and dried (25°C, 0.3 mmHg, 26 h) to give pure title salt 5a, 4.45 g (quantitative); mp 138-140°C. A 4.0 g sample was shipped to WRAIR as Code No. DJD-06-293, BL20345, on May 28, 1986.

Anal. Calcd for $C_{21}H_{23}NO_4S_2$ (417.53): C, 60.40; H, 5.55; N, 3.35; S, 15.36. Found: C, 60.12; H, 5.56; N, 3.42; S, 15.19.

1-Bis(4-methylthiophenyl)-3-dimethylaminoprop-1-ene Maleate (6, SNL-125, BL20336): - Aq formaldehyde (37%, 9.8 mL, 0.12 mol), sodium cyanoborohydride (4.4 g, 0.07 mol) and acetic acid (3.8 mL) were added to a cold (3°C) soln of the crude free base 5 (3.0 g, 0.01 mol) in HPLC-grade acetonitrile (150 mL). The mixture which exothermed to 10°C was stirred for 10 min. Dilute aq NaOH (375 mL water and 2 N NaOH, 4:1) was added and the soln was extracted with ether (300 mL). The organic layer was concd to an oil which was dissolved in ether (200 mL). The ether layer was washed with 2 N NaOH (150 mL) and with satd aq sodium chloride (3 x 150 mL), dried (K_2CO_3) and concd to a yellow oil. The oil was dissolved in methanol. The soln was filtered (celite) and the filtrate was stirred with maleic acid (1.15 g, 0.01 mol). The soln was concd to dryness and the residue was triturated with anhyd ether (250 mL). The off-white solid was collected, washed with anhyd ether (2 x 100 mL) and with petr ether (100 mL) and dried (25°C, 72 h) to give crude title compd, 2.7 g.

In the same manner, a total of 9.0 g (0.030 mol) of intermediate 5 was processed to give crude title compd, 8.5 g. This material (8.5 g) was dissolved in dichloromethane (300 mL), washed with 2 N NaOH (500 mL and 300 mL) and with deionized water (400 mL) and dried (K_2CO_3). The soln was concd to dryness. The residue was chromatographed over silica gel (100 g, J.T. Baker), eluting with dichloromethane (500 mL) to remove impurities. Elution with 1% MeOH gave slightly impure title compd free base, 1.5 g. Elution successively with 2% MeOH, 3% MeOH, 4% MeOH and 6% MeOH (500 mL each) gave pure title compd 6 free base, 4.25 g (56%) as a light yellow oil.

Conversion to the Maleate Salt 6: - A soln of maleic acid (1.35 g,11.6 mmol) in methanol (7 mL) was added to a clear soln of the free base (4.25 g, 12.9 mmol) in anhyd ether (425 mL). The mixture was stirred for 1 h. The white solid was collected, washed with anhyd ether (2 x 100 mL) and with petr ether (200 mL) and dried (25°C, 0.3 mmHg, 20 h) to give pure title compd, 4.8 g (93%); mp 145-147°C. A 4.5 g sample was shipped to WRAIR as Code No. DJD-06-288, BL20336, on May 28, 1986. The yield from the precursor free base 5, was 52%.

Anal. Calcd for $C_{23}H_{27}NO_4S_2$ (445.58): C, 61.99; H, 6.11; N, 3.14; S, 14.37. Found: C, 61.83; H, 6.30; N, 3.32; S, 14.50.

5.10 1-Bis(4-methylthiophenyl)-2-amidoximinoethylene Maleate (SNL-127, BL20354)

The two-step synthesis sequence is shown in Chart No. 7.

3-Bis(4-methylthiophenyl)acrylonitrile (1): - Concd hydrochloric acid (20 mL) was added to a warm (45°C) soln of 3-hydroxy-3-bis(4-methylthiophenyl)propionitrile (compound 3 of Chart No. 6, 10.6 g, 0.034 mol) in acetic acid (100 mL) and the mixture was stirred for 10 min (35-45°C). Most of the hydrogen chloride was removed (aspirator). The mixture was concd to dryness (aspirator) while maintaining the temp between 45-55°C (10 min). The oily residue was dissolved in ether (300 mL) and washed with 2 N NaOH (3 x 300 mL) followed by deionized water (3 x 150 mL, pH 7) and dried (Na_2SO_4). Concn (aspirator) gave the acrylonitrile 1 as a thick yellow oil (10.2 g) whose IR spectrum showed a strong nitrile absorption and TLC (Brinkmann 1% MeOH-$CHCl_3$) showed a single spot with higher Rf than the starting hydroxynitrile. This material was used directly in the next step.

Conversion to the Amidoxime 2, Free Base: - A soln of potassium hydroxide (14 g, 86% pure, 0.215 mol) in anhyd alcohol (250 mL) was added in 25 min to a suspension of hydroxylamine hydrochloride (14 g, 0.21 mol) in anhyd alcohol (250 mL) containing phenolphthalein indicator. The soln was filtered and the collected salt was washed with alcohol (50 mL). The acrylonitrile 1 (10.2 g, 32.30 mmol) was added to the filtrate and the mixture was refluxed (steambath) while removing part of the alcohol (200 mL) by distillation. The mixture was refluxed for 18 h, concd to dryness and redissolved in warm alcohol (200 mL, 50°C). The soln was allowed to cool to room temp and stirred for 1 h. The off-white solid was collected, washed with anhyd ether(2 x 100 mL) and with petr ether (100 mL) and air-dried (25°C, 2 h) to give the title amidoxime 2 free base, 5.8 g (52%), mp 156-159°C.

Conversion of the Amidoxime to the Maleate Salt (2, SNL-127): - Maleic acid (2.3 g, 0.02 mol) was added to a warm (50°C) suspension of the amidoxime free base 2 (5.8 g, 0.017 mol) in methanol (200 mL) to give yellow soln. This soln was charcoaled, filtered (celite) and concd to dryness. The residue was triturated with anhyd ether (300 mL) for 30 min. The solid was collected by filtration, washed with anhyd ether (2 x 100 mL) and with petr ether (100 mL) and dried (25°C, 1 h) to give crude title salt, 7.35 g, mp 142-144°C.

This material was slurried with deionized water (300 mL) for 15 min, filtered, washed successively with deionized water (4 x 50 mL), anhyd ether (4 x 50 mL) and petr ether (2 x 50 mL) and dried (25°C, 30 min). This solid was dissolved in hot 60% aq ethanol (EtOH-H_2O, 4:6, 56 mL). The soln was filtered, cooled to room temp and stirred for 16 h. The solid was collected, washed with anhyd ether (4 x 50 mL) and with petr ether (2 x 50 mL) and dried (80°C, 0.3 mmHg. 2 h) to give pure title amidoxime maleate salt 2 as a light yellow solid, 5 g (64% from 2 free base); mp 145-147°C. A 4.0 g sample was shipped to WRAIR on May 28, 1986 as Code No. DJD-06-295, BL20354.

Anal. Calcd for $C_{21}H_{22}N_2O_5S_2$ (446.53): C, 56.48; H, 4.97; N, 6.27; S, 14.36. Found: C, 56.58; H, 4.95; N, 6.37; S, 14.43.

5.11 1-(4'-Bromophenoxy-4-phenyl)-1-(4-chlorophenyl)-2-amidoximino-ethylene Maleate (SNL-128, BL21780)

The synthesis sequence is shown in Chart No. 8.

4-(4'-Bromophenoxy)benzaldehyde (1): - The potassium salt of 4-bromophenol was prepared by adding 4-bromophenol (95.5 g, 0.55 mol) to a soln of potassium hydroxide (36.2 g, 86% pure, 0.55 mol) in methanol (380 mL). The soln was stirred for 30 min, and concd to dryness (50°C, aspirator). The residue was dried at room temp and 1 mmHg for 20 h and mixed with 4-fluorobenzaldehyde (60 g, 0.48 mol) in dimethylformamide (400 mL) under nitrogen. The mixture was refluxed (oil bath, 160-170°C) for 1.75 h. DMF was largely removed at 45-55°C/1 mmHg and the residue was stirred with a mixture of ether (500 mL) and water (500 mL). The ether layer was washed with 2 N NaOH soln (3 x 250 mL) and with deionized water (3 x 250 mL, pH 7), and dried (Na_2SO_4) with charcoaling. The soln was filtered (celite) and the residue was triturated with hexanes (300 mL). The off-white solid was collected by filtration and dried (25°C, 16 h) to give crude title compd, 95 g. This material was chromatographed over J.T. Baker silica gel (900 g), eluting with ether-petr ether (5:95, 4 L and 1:9, 3 L) to give pure title compd, 87 g (65%), mp 66-68°C.

Anal. Calcd for $C_{13}H_9BrO_2$ (277.12): C, 56.34; H, 3.27; Br, 28.84. Found: C, 56.56; H, 3.17; Br, 28.70.

4-(4'-Bromophenoxyphenyl)-4-chlorobenzophenone (2): - A soln of 4-chlorophenylmagnesium bromide in ether (0.16 mol, 165 mL, 1 M) was added slowly to a soln of phenoxybenzaldehyde 1 (45 g, 0.16 mol) in dry anhyd ether (400 mL). The mixture was stirred at room temp for 30 min and poured into cold dil hydrochloric acid (concd $HCl-H_2O$, 1:4, 500 mL). The organic layer was washed successively with water (200 mL), satd aq sodium bicarbonate (2 x 250 mL) and water (2 x 250 mL, pH 7) and dried (Na_2SO_4) with charcoaling. The soln was filtered (celite). The filtrate, combined with the filtrate from another experiment (40 g), was concd to give crude intermediate diarylcarbinol, 119 g, as an oil. This material was purified by column chromatography over EM silica gel (950 g) eluting with ether-petr ether (5:95, 2 L and 1:9. 2 L) to remove impurities. Elution with ether-petr ether (15:85, 2 L and 1:4, 2 L) gave slightly impure carbinol, 47 g. Elution with ether-petr ether (3:7, 2 L and 1:1, 2 L) gave pure carbinol, 65 g (54%).

Oxidation of the Carbinol to Ketone: - Glacial acetic acid (21.5 mL) and concd sulfuric acid (31.7 mL) were added to aq sodium dichromate soln (22.9%, 111 mL) at room temp. The mixture exothermed to 50°C and was cooled to 30°C. A soln of the carbinol (65 g,0.17 mol) in benzene (950 mL) was added (40 min) to the mixture while maintaining the temp between 30-45°C. The mixture was stirred for 1 h at 44-48°C. The organic layer was separated and the aq layer was reextracted with benzene (2 x 150 mL). The combined organic layers were washed successively with water (2 x 250 mL), satd sodium bicarbonate soln (4 x 250 mL) and water (3 x 500 mL, pH 7), dried (Na_2SO_4) with charcoaling and filtered (celite). The volume was reduced to ca. 500 mL and diluted with hexanes (1 L). The off-white solid was collected and dried (25°C, 72 h) to give crude title compd, 59.5 g (91%), mp 156-158°C. An analytical sample, prepared by recryst from benzene-hexanes (1:1) had mp 157-159°C.

Anal. Calcd for $C_{19}H_{12}BrClO_2$ (387.66): C, 58.86; H, 3.12; Halogen, 18.30. Found: C, 59.06; H, 3.24; Halogen, 18.42.

3-(4'-Bromophenoxy-4-phenyl)-3-(4-chlorophenyl)-3-hydroxypropionitrile (3): - A mixture of sodium amide (6 g, 0.15 mol), acetonitrile (9 mL, 7.1 g, 0.17 mol) and dry benzene (450 mL) was refluxed 10 min and cooled to 50°C. A soln of benzophenone 2 (30 g, 0.08 mol) in dry benzene (300 mL) was added at once and the mixture was refluxed for 5 min. Additional acetonitrile (2 x 9 mL) was added and heating was continued 15 min. The mixture was cooled and poured into cold water (1.5 L). The aq layer was extracted with ether (2 x 300 mL) and the combined organic layers were washed with satd brine (2 x 500 mL), dried (Na_2SO_4) with charcoaling and filtered (celite). The filtrate was concd to give crude title compd, 35 g. This was purified by column chromatography over J.T. Baker silica gel (500 g), eluting with benzene (2 L) to remove unreacted ketone, 6 g. Elution with 5% MeOH-CH_2Cl_2 (2 L) and 7% MeOH-CH_2Cl_2 (500 mL) gave partially purified title compd, 23 g (87%). This material was dissolved in hot

benzene (250 mL) and filtered. The volume was reduced to 100 mL and diluted with hexanes (300 mL). The solid was collected by filtration, washed with hexanes (2 x 75 mL) and dried (40°C, 0.3 mmHg, 16 h) to give pure title compd 4, 20.1 g (75%), mp 150-153°C. A total of 29 g of the title compd was prepared in this manner.

Anal. Calcd for $C_{21}H_{15}BrClNO_2$ (428.71): C, 58.83; H, 3.53; N, 3.27; Halogen, 16.54. Found: C, 59.01; H, 3.54; N, 3.18; Halogen, 16.86.

3-(4'-bromophenoxy-4-phenyl)-3-(4-chlorophenyl)acrylonitrile (4): - Phosphorus pentoxide (60 g, 0.42 mol) was added to a hot soln of hydroxynitrile 4 (25 g, 0.058 mol) in dry benzene (1 L). The mixture was refluxed (7 min), additional phosphorus pentoxide (40 g, 0.28 mol) was added and heating continued (7 min). the mixture was cooled to 40°C and filtered (celite). The gummy residue was triturated with warm benzene (2 x 100 mL). The combined benzene layers were concd to dryness and the residue was dissolved in anhyd ether (200 mL). The soln was filtered (celite) and concd to give the title compd 5, 22.9 g (96%), as yellow syrup.

1-(4'-Bromophenoxy-4-phenyl)-1-(4-chlorophenyl)-2-amidoximino-ethylene Maleate (5): - A soln of potassium hydroxide (40 g, 86%, 0.61 mol) in anhyd alcohol (500 mL) was added over 30 min to a suspension of hydroxylamine hydrochloride (40 g, 0.57 mol) in anhyd alcohol (750 mL) containing phenolphthalein. The mixture was stirred for 30 min and filtered. The nitrile 4 (22.9 g, 0.056 mol) was added to the filtrate and the mixture was refluxed (steam bath) while removing part of the alcohol (500 mL) by distillation. The mixture was refluxed for 30 h and concd to dryness, codistilled with hexanes (2 x 150 mL) and redissolved in anhyd ether (750 mL). The soln was filtered (celite) and concd to dryness to give the crude free base as a light yellow oil, 26 g.

Conversion of the Free Base to Maleate Salt (5, SNL-128): - Maleic acid (10 g, 0.086 mol) was added to a soln of the free base (26 g) in methanol (100 mL). The soln was stirred (5 min), concd and the residue was triturated with anhyd ether (450 mL). The beige solid was collected, washed with anhyd ether (2 x 150 mL) and with petr ether (150 mL) to give crude title salt, 25 g. This material was slurried with deionized water (500 mL) for 10 min. The off-white solid was collected, washed with anhyd ether (3 x 150 mL) and with petr ether (2 x 150 mL) and dried (25°C, 1 h) to give partially purified salt, 12.4 g, mp 140-145°C dec. The salt was dissolved in hot 60% aq ethanol (75 mL). The soln was filtered and cooled to room temp. The solid was collected, washed with anhyd ether (4 x 50 mL)

and with petr ether (2 x 50 mL) and dried (80°C, 0.3 mmHg, 2 h) to give pure title maleate salt 6, 8.1 g (26%), mp 150-153°C dec. A 7.5 g sample was shipped to WRAIR on July 21, 1986 as Code No. DJD-07-27, BL21780.

Anal. Calcd for $C_{25}H_{20}BrClN_2O_6$ (559.80): C, 53.63; H, 3.60; N, 5.01; Halogen, 12.67. Found: C, 53.44; H, 3.65; N, 5.11; Halogen, 12.86.

5.12 1-(4'-Bromophenoxy-4-phenyl)-1-(4-chlorophenyl)-3-dimethylaminoprop-1-ene Maleate (SNL-129, BL22205)

The essentially one-step synthesis sequence is shown in Chart No. 9.

n-Butyllithium (31 mL, 1.6 M,0.049 mol) was added to a suspension of (2-dimethylaminoethyl)triphenylphosphonium bromide (20.3 g, 0.049 mol) in dry tetrahydrofuran (450 mL) under nitrogen. The temp was maintained between 3-5°C (ice-bath). The mixture was stirred 10 min at 3-5°C. A soln of 4-(4'-bromophenoxy)-4-chlorophenylbenzophenone (compound 2, section 5.11, 15.4 g, 0.04 mol) in dry THF (250 mL) was added in 15 min while the temp was maintained between 3-5°C. The mixture was stirred (30 min), warmed to room temp, stirred for 1 h, refluxed for 2 h and cooled to 15°C. Water (15 mL) was added and the mixture was concd to dryness (50°C, aspirator). The residue was treated with dil hydrochloric acid (concd HCl-H_2O, 1:3, 300 mL) to give an oil. This was triturated with ether (2 x 500 mL) and the triturate was discarded. The residue was dissolved in dichloromethane (600 mL). The soln was washed with 2 N NaOH (3 x 300 mL) and with water (300 mL), dried (K_2CO_3) with charcoaling, filtered (celite) and concd to dryness. The residue was dissolved in methanol (100 mL) and maleic acid (7 g, 0.06 mol) was added. The clear soln was diluted with anhyd ether (1 L). The solid was collected, washed with anhyd ether (2 x 100 mL), petr ether (100 mL) and dried (25°C, 2 h) to give crude title maleate salt 3, 12 g.

The salt (12 g) was dissolved in dichloromethane (500 mL). The soln extracted with 2 N NaOH (4 x 250 mL), satd brine (250 mL) and water (250 mL) and dried (K_2CO_3) with charcoaling. The soln was filtered (celite), concd (10 g) and chromatographed over J.T. Baker silica gel (150 g), eluting with dichloromethane (2 L) to remove impurities. Elution with 1% MeOH-CH_2Cl_2 (2.5 L) gave slightly impure product (0.5 g, discarded). Elution with 2%, 4% and 6% MeOH in

CH_2Cl_2 (1 L each) gave the title compd free base (7.98 g). This material was rechromatographed over J.T. Baker silica gel (80 g) to remove polar impurities to give purified free base as a light yellow oil. A soln of the oil in anhyd ether was charcoaled, filtered (celite) and the filtrate was refiltered (gravity). The soln was concd to give pure free base, 7.38 g (42%).

Conversion of the Free Base to the Maleate Salt (3, SNL-129): - A soln of maleic acid (1.74 g, 0.015 mol) in methanol (12 mL) was added to a light-yellow soln of the pure free base (7.38 g, 0.017 mol) in anhyd ether (200 mL). The mixture was stirred for 1 h and filtered. The white solid was washed with anhyd ether (4 x 150 mL) and with petr ether (2 x 150 mL) and dried (25°C, 0.3 mmHg, 24 h) to give pure title maleate salt 3, 7.3 g (87%), mp 175-179°C (shrinks between 145-155°C). A 6.5 g sample was shipped to WRAIR as Code No. DJD-06-32, BL22205, on August 7, 1986.

Anal. Calcd for $C_{27}H_{25}BrClNO_5$ (558.85): C, 58.02; H, 4.51; N, 2.51; Halogen, 12.68. Found: C, 57.93; H, 4.61; N, 2.70; Halogen, 12.73.

5.13 1-(4'-Bromo-4-biphenylyl)-1-(4-chlorophenyl)-3-dimethylamino prop-1-ene Maleate (SNL-130, BL24003)

The synthesis sequence is shown in Chart No. 10.

1-(4-Bromo-4-biphenylyl)-4-chlorobenzophenone (1): - A mechanically stirred cold suspension (0°C, ice-salt bath) of anhyd aluminum chloride (71.5 g, 0.536 mol) and 4-bromobiphenyl (125 g, 0.536 mol) in carbon disulfide (215 mL) was treated with 4-chlorobenzoyl chloride (93.8 g, 0.536 mol) added at a rate to maintain the temp between 0°-5°C. The mixture was allowed to warm slowly to room temp, then refluxed 6 h (steam bath). Carbon disulfide was removed by distillation. The solid residue was cooled to 0°C and ice-cold 5% aq hydrochloric acid (1 L) was added over 30 min with stirring. The wet crude product was separated and slurried with chloroform to remove the unreacted starting materials. The washed solid was collected, washed successively with chloroform (1 L total), 10% aq sodium hydroxide and then with water until the washes were neutral. This material was air-dried (159 g, 80%) and recryst from a boiling mixture of methoxyethanol (2 L) and toluene (1 L). After cooling to room temp, the mixture was filtered to give once-recryst benzophenone 1, 136 g, mp 180-198°C. This wide melting product was recryst from methoxyethanol (1.4 l) to give pure benzophenone 1, 114 g (58%), mp 197-200°C; lit. 194°C, ref. 3c.

Anal. Calcd for $C_{19}H_{12}BrClO$ (371.45): C, 61.38; H, 3.26; Halogen, 19.09. Found: C, 61.14; H, 3.15; Halogen 19.06.

1-(4'-Bromo-4-biphenylyl)-1-(4-chlorophenyl)-3-dimethylamino-prop-1-ene Maleate (2, SNL-130)

n-Butyllithium in hexane (1.6 M, 28 mL) was added dropwise to a suspension of 2-dimethylaminoethyltriphenylphosphonium bromide (16.3 g, 0.0393 mol) in dry tetrahydrofuran (100 mL), while maintaining the temp at ca. 0°C. After stirring for 45 min at this temp, a soln of intermediate 1 (14.6 g, 0.0393 mol) in warm tetrahydrofuran (200 mL) was added dropwise while maintaining the temp at ca. 0°C. The mixture was allowed to warm to 20°C, refluxed 4.5 h, stirred at room temp overnight, cooled (ice-bath) and quenched by adding 2 N hydrochloric acid (30 mL) and water (200 mL). The mixture was thoroughly extracted with chloroform (700 mL total). The extract was washed with water, 2 N sodium hydroxide (2 x 150 mL) and with water until the water washes were neutral. The organic layer was dried ($MgSO_4$) and the solvent was evaporated (aspirator). The solid residue (product and a trace of compound 1 by TLC) was stirred with ether (500 mL). The mixture was filtered to remove benzophenone 1, 1.2 g. A soln of oxalic acid (3.25 g, 0.0361 mol) in ether (30 mL) was added to the ethereal filtrate. The crude oxalate salt was separated, 17.4 g (93% based on recovered 1), mp 128-176°C. A portion of this oxalate salt (9.8 g, 0.019 mol) was suspended in chloroform (500 mL) and washed with excess 2 N sodium hydroxide to give a clear chloroform soln (wash discarded). The organic layer was separated, washed with water, dried ($MgSO_4$) and the solvent was evaporated (aspirator). The title compound 2, free base, was obtained as a thick oil, 8.0 g. This oil was dissolved in ether (150 mL) and treated with a soln of maleic acid (2.15 g, 0.0185 mol) in methanol (30 mL). The mixture was cooled, filtered and dried (60°C, 0.3 mmHg) to give the maleate as an off-white powder, 7.25 g, mp 190-194°C. This material (6 g, impure by TLC) was dissolved in dichloromethane (600 mL) and the soln was washed with 2 N sodium hydroxide (4 x 250 mL) to regenerate the free base (wash discarded). The organic layer was washed with brine and with water and dried (K_2CO_3). The solvent was evaporated to recover the free base 2 (6 g). This material, still not pure by TLC, was chromatographed using silica gel (60 g, J.T. Baker). The column was eluted with CH_2Cl_2 (2 L), followed by CH_2Cl_2-MeOH mixtures (2% MeOH, 3% MeOH and 4% MeOH, balance CH_2Cl_2). The product-containing fractions were evaporated to give the title free base 2, 3.75 g (79%) as a light-yellow oil.

Conversion of the Free Base to the Maleate Salt 2: - A soln of maleic acid (0.93 g, 8 mmol) in methanol (6 mL) was added to a soln of the pure free base (3.74 g, 8.7 mmol) in anhyd ether (200 mL). The mixture was stirred for 30 min and filtered. The salt was collected, washed with anhyd ether (4 x 125 mL) and with petr ether (2 x 125 mL) and dried (24 h, 0.3 mmHg, 18 h) to give pure title maleate salt 2, SNL-130, 4.2 g (97%), mp 200-205°C dec. A total of 4.8 g of pure title compound was prepared in the same manner. A 4.5 g sample was shipped to WRAIR on August 28, 1986 as Code No. DJD-07-44, BL24003.

Anal. Calcd for $C_{21}H_{23}BrClNO_4$ (542.85): C, 59.73; H, 4.64; N, 2.58; Halogen, 13.06. Found: C, 59.64; H, 4.79; N, 2.72; Halogen, 13.22.

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3) a. "The Efficacy of a Novel Compound, (E)-1-(4'-bromo-4-biphenyl)-1-(4-chlorophenyl)-3-dimethylaminoprop-1-ene against Trypanosoma cruzi in mice', P.A. Barrett et.al., Experientia 38 (1982), Birkhauser Verlag. CH 4010 Basel Switzerland, p. 339.

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b. "Antituberculous Drugs and Kala-azar", W. Peters et.al., The Lancet, p. 304, August 8, 1981 (two communications).

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6) "The Orientation of P-Methoxydiphenyl in the Friedel and Crafts Reaction", L.F. Fieser and C.K. Broadsen, J. Am. Chem. Soc., 58, 1738 (1936).

7) "4-(p-Hydroxyphenyl)-cyclohexanecarboxylic Acid and Derivatives", W.S. Johnson et.al., ibid 68, 1648 (1946).

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APPENDIX A

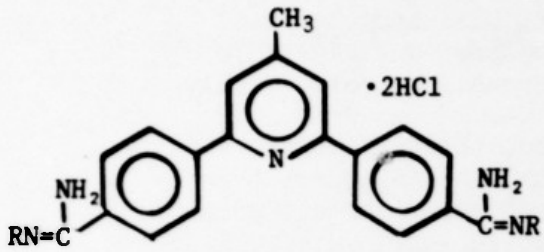
FIGURE A-1

SELECTED ACTIVE ANTITRYPANOSOMAL STRUCTURES

From Prior Contract (Ref. 1)

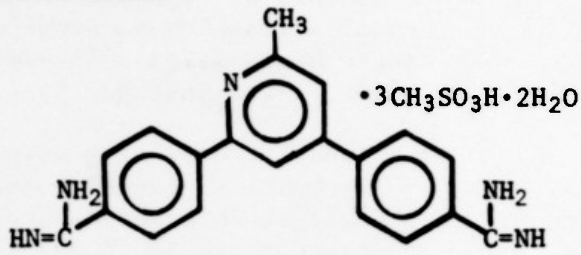
(T. rhodesiense, See Table 2, Section 2.2)

A. Bis(aryl) Heterocycles

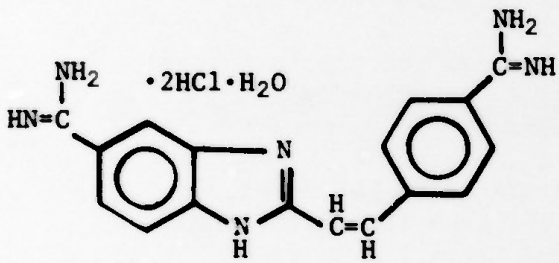


SNL-28, R = OH, WR 248,396

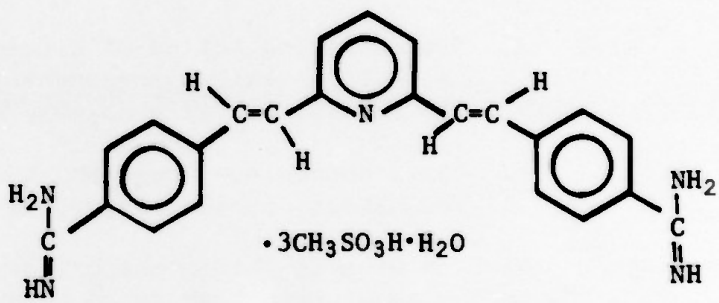
SNL-29, R = H, WR 248,535



SNL-54, WR 250,262

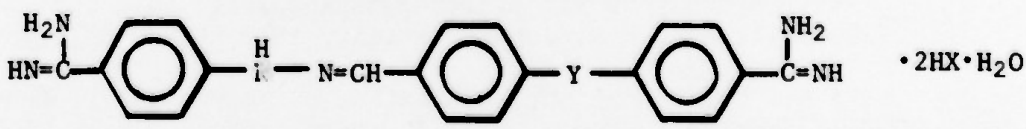


SNL-47, WR 249,698



SNL-107, WR 252,070

B. HOE 668 (SNL-77) and a Thio Analog (SNL-96)



SNL-77, Y = O, WR 245,720, 2HX = Dimaleate

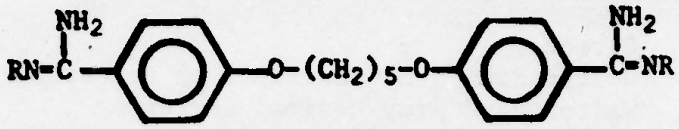
SNL-96, Y = S, WR 251,336, 2HX = Dihydrochloride

Continued

APPENDIX A

FIGURE A-1 (Continued)

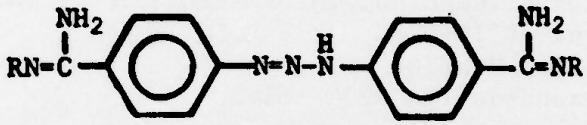
C. Commercial Bis(amidines) and their Bis(amidoxime) Analogs



SNL-63, R = OH, WR 250,385 •2HCl•0.5H_2O

SNL-64, R = H, WR 4,931 •2HCl (Pentamidine)

WR 4,931, Commercial: Pentamidine Diisethionate



SNL-67, R = OH, WR 250,483 •Dimaleate

SNL-68, R = H, WR 27,800 •Dimaleate (Diminazene; Berenil)

WR 27,800, Commercial: Diminazene(Berenil) Diaceturate

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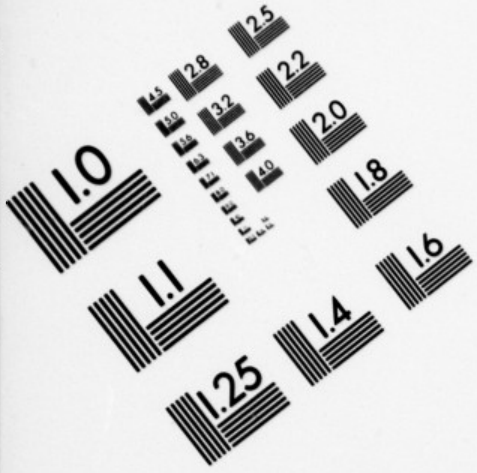

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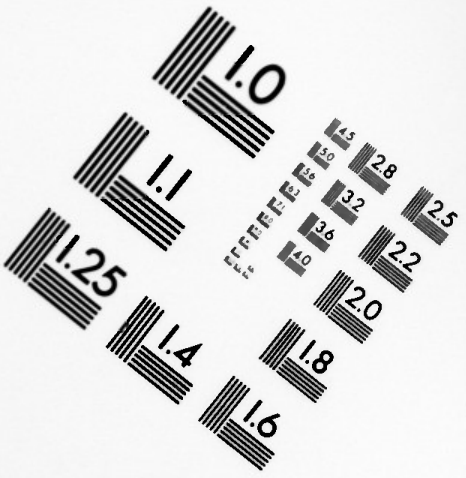

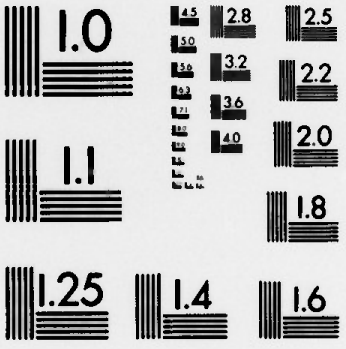

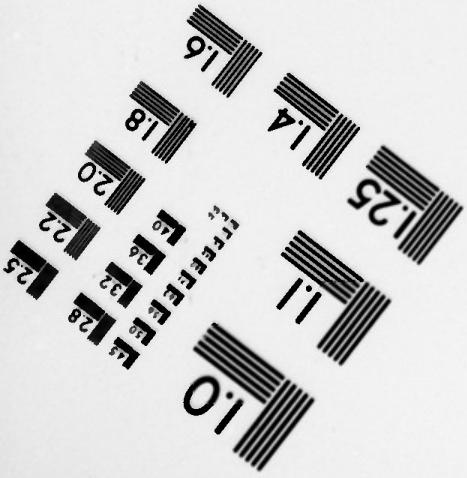

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24 JUL 1992

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